DECEMBER 1961

# BRAIN

VOL. 84, PART 4.

## HEAD'S PARADOXICAL REFLEX[1]

BY

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WHEN Henry Head was a young man, after he had taken his Natural Sciences Tripos at Cambridge and before he did his clinical medicine at University College, he went to study in Hering's laboratory in the German University of Prague. Hering together with Breuer, had in 1868 described what is now known as the "Hering-Breuer Reflex." The part of it in which I am interested is, that if the lungs are inflated then the animal ceases to make inspiratory movements. Before going into the details of this particular part of Head's work we may note that in this paper there is a very curious mixture of the antique and the modern. For example it is surprising to find oneself referred, in a scientific paper (Head, 1889), to the "woodcut on page 31." But every now and then a quite strikingly modern phrase turns up, thus when he is referring to the fact that the animal will in the end take an inspiration after a long period of apnœa (lack of breathing) due to inflation, he says, "I shall call this phenomenon the negative after-action." That has a modern ring but Head shows that he is a little cynical about jargon of this type, for he adds, and this spoils it all, "For want of a better term." And then at one point in his work Head was faced with the problem of studying what happened in an animal when one lung was either inflated or deflated for a very long period while the animal was adequately oxygenated. He was not appalled by what was technically an extremely difficult problem and he made for himself a cuffed endobronchial tube. I have asked various of my anæsthetic colleagues about the date at which cuffed endobronchial and endotracheal tubes were introduced, and they have all put dates about the 1930s. Head had done this well before 1889.

In wanting to study the "Hering-Breuer Reflex" Head points out in his paper that the methods of recording respiration at this time were not very

[1]Paper read at the Henry Head Centenary Celebrations at the London Hospital, August 31, 1961.



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suitable to the purpose. He notes that the Marey Tambour attached to the trachea, the stethograph around the chest or Knoll's Method (1874) (an animal in an airtight box, with a tracheotomy tube opening to the outside) are none of them suitable for recording the animal's response to inflation of the lungs. None of these methods, whether they record changes in pressure or volume, will distinguish between the passive consequence of lung inflation, and the reflex response of the animal's musculature, and so he devised the preparation which is known as the "Head's diaphragm slip preparation." He says, "When the diaphragm of the rabbit is viewed from the abdominal side the strong development of the two anterior limbs is very noticeable." He appreciated that if he made a suitable preparation of the anterior limb (the diaphragm slip) he could record how this sample of the diaphragm muscle was responding to inflation of the lung.

Fig. 1A shows his first adequate tracing of the ordinary Hering-Breuer Reflex, together with the inflation pressure applied. With a pressure of 7 mm.Hg, the diaphragm slip relaxes, and no inspiratory movements occur until the pressure is removed.

In the experiments which he was performing on rabbits, he was concerned with cutting the vagi because the sensory pathway for this reflex runs through the two vagus nerves, but he needed to cut them without stimulating them in any way. He points out that Gad (1880) had shown that the sensory activity of the vagi could be paralysed by freezing them on thermodes (copper wires attached to freezing mixtures). While using the freezing method he made the following important observation. After he had paralysed the vagi by freezing he studied the stages of recovery, and he said:

"Firstly a considerable time (10 minutes) during which inflation of the lungs produces no effect at all—the vagi have lost their conducting power. Secondly a stage during which an inflation produces an inspiratory effect (fig. 1B); and thirdly one in which inflation of the lungs produces the usual inhibition of inspiration. If, however, the vagi are allowed to remain some time (10 seconds) on the thermodes, this *paradoxical effect* ceases to make its appearance, when the nerves are removed from the freezing apparatus."

And later he says: "That this phenomenon is due to the vagi and not to some other nerve is proved by its immediate disappearance when the vagi are cut by scissors."

Figs. 1A and B show the comparison of the two different effects: the normal effect giving relaxation, the abnormal effect with the semi-frozen vagi when inflation causes increased respiratory tone.

This paradoxical effect which Head described obviously troubled him a very great deal, and I think two very important points come out of this rather academic piece of information. The first is, that Head clearly appreciated very deeply what the nature of a reflex was. The anatomy of the reflex arc was within reason well established at this time, but as far as

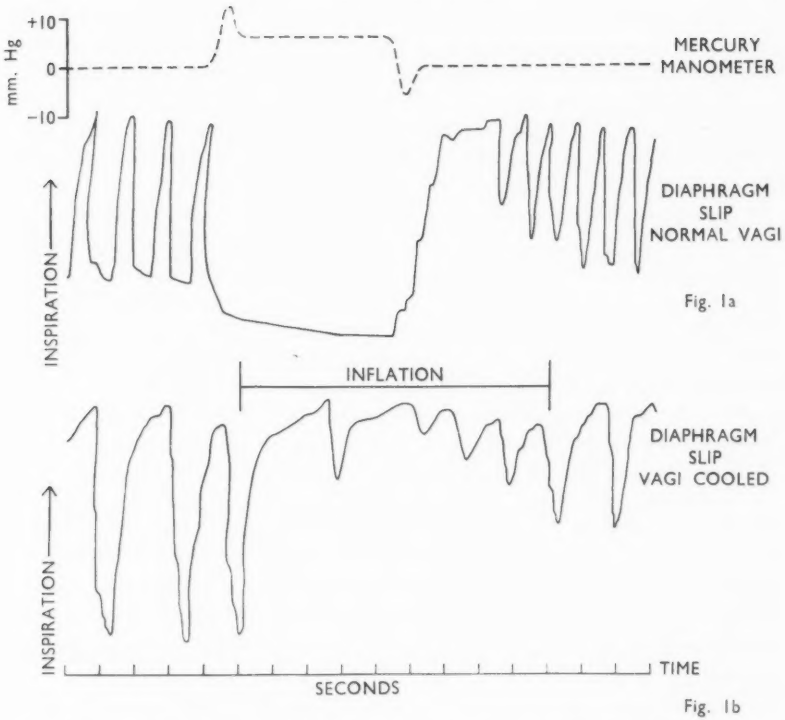


FIG. 1A.—Hering-Breuer Reflex, illustrated by Head, 1889, Plate ii, curve iii. Upper trace records tracheal pressure, using a mercury manometer; the ordinate scale, not given in Head's paper, assumes that the plates are life-size reproductions and that a U-tube manometer was used.

FIG. 1B.—Plate i, curve vi (Head, 1889). Head's Paradoxical Reflex showing the increase in inspiratory tone when the lungs are inflated after the vagi have been cooled. Both figures are re-drawn from Head's paper, with the same relative increase in the ordinate scale.

I know, no one had appreciated as clearly as Head that a reflex was concerned with maintaining the *status quo* in the animal. It restored the animal to normal—or in modern jargon—it was a negative feed-back mechanism. And Head was extremely disturbed to find an instance, even with the abnormal vagi, when inflation of the lungs produced a situation where the animal was, as it were, encouraging inflation.

The second point which came out of this work was this: Head passed on to us a method which is still in use by physiologists, the differential paralysis of function, by taking sensory nerves to particular low temperatures.

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We would say nowadays that the sensory side of the Hering-Breuer Reflex is carried in large myelinated fibres, with rapid conduction velocities which lose their function between 15 and 9° C., whereas the Head Reflex is carried in small unmyelinated fibres with slower conduction velocities which cease to conduct at considerably lower temperatures (between 11 and 5° C.) (Widdicombe, 1954). But this method—this tool—has been of value and has been employed ever since.

I now pass from Head's work to some work in which I have been interested, because I think there may be a connexion. My own particular line of interest has been respiration in the newborn baby, and I have used what is essentially the method of Knoll in recording respiration in the baby. The baby is enclosed in an airtight box and both his mouth and nose, instead of an endotracheal tube, is open to the outside world (with the face sealed into the box with a soft pneumatic cuff). When he breathes in, he swells, and a strain gauge records the change of pressure in the box and that can be calibrated in terms of volume.

When I was in San Francisco with Dr. Julius Comroe two years ago, I was very anxious to measure the cardiac output in the newborn baby, and I discussed with him the need for doing this, saying that the methods available were hardly ethical for normal newborn babies, to which he replied "Oh, well, use the method of Lee and DuBois" (1955).

Lee and DuBois working with co-operative adult subjects asked them to take a deep breath of a particular gas mixture at a given moment, and then to hold their breath.

I thanked Dr. Comroe for his advice but asked him how I was going to get a baby, at request, to take a deep breath and hold it, and he said "That was my problem."

More to prove that it couldn't be done, than for any other reason, we (Cross, Klaus, Tooley and Weisser, 1960) tried tentatively the effect of inflating the newborn baby's lungs. The method used was to have a mask over the baby's face attached to a bag, such as the anæsthetists use. A squeeze on the bag at a given moment and blocking up the exit tube caused inflation. When inflated the baby swelled but also gave the appearance that it might have taken a breath at this time. If the baby did take a breath then that was a paradoxical effect. But of course, just as Head criticized the method of Knoll, saying it was unsuitable for recording the response to inflation, so we needed to record the baby's response in greater detail.

Diaphragm slip preparations are not available in the newborn baby and hence we tried to find out what the musculature of respiration was doing by putting an œsophageal tube down the baby. An œsophageal tube records quite faithfully the intrapleural pressure (Leathart and Dornhorst, 1952), and if indeed the baby had taken a breath in at this time then one

would expect this œsophageal pressure to go deeply negative, and we found that this was indeed the case.

Inspiratory activity in response to inflation of the lungs was clearly highly abnormal; Head had only found it when he had half-frozen the vagi, and we were particularly excited to find it in newborn babies. The newborn baby has been born with totally collapsed lungs, and any response one finds which promotes expansion of the lungs is of considerable interest. We speculated that possibly this response might disappear in the first few days of life, and so we looked at the occurrence of the response in babies of different ages and found that the gasp in response to inflation occurred significantly less frequently with increasing age.

If one reads the books of obstetrics, pædiatrics and physiology, they rather gloss over the mechanism whereby the baby takes its first breath. Various facts are paraded showing that the fœtus has a normal type of respiratory centre and so on, but the main issue is always avoided, which is that the lungs have got fluid in them at the time of birth and they are very easy to expand with fluid, but for reasons of surface tension are very difficult to expand with air. It requires a much higher pressure to expand them with air, and it is begging the question to point out that the fœtus makes slight respiratory movements. What we want to know is how the newborn baby makes *vigorous* inspiratory movements. The gasping response on the part of the baby is indeed a vigorous inspiratory movement—giving negative pressures up to 40 cm. of water, while normal respiratory activity in the expanded lung requires only about 6 cm. of water pressure.

There is one phenomenon about the birth of a newborn baby which is known to everyone, and that is the cry which occurs so soon after a normal birth. Many interpretations have been put on this cry, but they are generally the wrong ones. The cry tells the psychiatrist and the novelist quite different things from what it tells the physiologist, which is that the baby has managed to get a lot of air in its lungs, for the noise of crying is an expiratory activity. Thus when a baby cries it has got quite a lot of breath inside it, and it has made vigorous inspiratory efforts. I suggest the possibility that this gasping response in the newborn baby is in fact Head's Paradoxical Reflex, and it is by its mediation we each took our first breath.

Head said of it: "I am totally at a loss to account for its appearance."

I suggest the possibility that Head's Paradoxical Reflex is vestigial in the adult, a phenomenon which is only uncovered by special physiological techniques, but may be of quite vital importance in the newborn.

In conclusion I think it speaks very strongly for the creative activity of Head that I and my colleagues in this hospital should still be working on a subject which he uncovered over seventy years ago.

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And on a more personal note it gives me very great pleasure that some of this work should be attempted in his old hospital which he served so well.

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# HENRY HEAD'S WORK ON SENSATION[1]

BY

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HENRY HEAD published some twenty papers on various aspects of sensation between 1886 and 1921. This year of space travel is an appropriate time to recall one of his lesser known communications; in 1918 he reported that a test pilot had experienced graying of vision followed by fainting while flying in a small, horizontal, banked circle in which the positive acceleration reached 4·5 g. He wrote, "this pilot found experimentally that whenever the acceleration (g) was pushed up to a high figure, he experienced the characteristic darkening of the sky which was preliminary to fainting." This was the first account of the effect of positive acceleration on pilots in flight.

Head's earlier work on sensation was concerned with the pain of visceral disease and with zoster, but his major contribution was a series of papers which appeared between 1905 and 1918, and contained his observations and views on the afferent nervous system. His ideas developed from clinical studies on patients with lesions affecting the sensory pathways at different points from peripheral nerve to cerebral cortex, and from his own experiences during the celebrated experiment in human nerve division. In this work he was assisted by Theodore Thompson and James Sherren, physician and surgeon to this hospital, by Rivers, fellow of St. John's College, Cambridge, and by Gordon Holmes. The major papers from this series were collected and published as "Studies in Neurology" in 1920, together with an epilogue and appendix in which he dealt with some of the criticisms of his work and theories.

Head's observations and ideas were subjected to stern criticism from contemporary workers such as Von Frey, Trotter and Davies, and Boring. In later years some textbooks of physiology for students described the afferent system in Head's terms, but there was always considerable scepticism about his views in the minds of clinicians and physiologists. Walshe (1942) published a detailed criticism of his observations and theories, and this served to eclipse them further. During the past decade, however, neurophysiologists have shown a new interest in Head's ideas

[1]Paper read at the Henry Head Centenary Celebrations at the London Hospital, August 31, 1961.

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on the modification of sensory impulses and duality in the afferent system, and it is no exaggeration to say that his reputation stands higher than at any time since his death.

When Head began his studies on sensation the idea was widely held that man is endowed with specific sense organs capable of responding to each known sensory experience. The impressions produced by stimulation of end-organs were thought to be transmitted unchanged by specialized nerve fibres and a single spinal tract, directly or through intermediate cell systems, to the appropriate cortical centres, where they evoked some single sensory experience. It was also thought that there were exact quantitative relations between stimulus and sensation. This conception of the afferent system is particularly associated with the name of Von Frey. From his studies on peripheral nerve injuries, and the results of nerve division in his own arm, Head formed the view that these ideas were wrong; he wrote, "Between the act of physical stimulus and the act of sensation there lies a multitude of physiological transformations" (p. 10[1]). However, it may be helpful to recall the intellectual and neurological climate prevailing at the time he was working before describing and discussing his work. It is just one hundred years since the celebrated controversy between Bishop Wilberforce and Huxley at an Oxford meeting of the British Association, and Head was evidently much influenced by evolutionary theory. The teachings of Hughlings Jackson, another physician to this hospital, also affected his thinking profoundly. Thus he wrote, "Sensation was originally a vague undifferentiated state, and progress has taken place by the slow acquirement of more specific reactions. This has occurred not only in consequence of the development of sense organs of higher capacity, but, to an even greater extent, by increasingly perfect integration of afferent impulses at various sensory levels . . . in man sensation is a highly differentiated reaction to physiological processes which have undergone profound transformations on their way from peripheral end-organs to the highest receptive levels" (p. 10). On the neurological side there was a substantial degree of anatomical ignorance, and this led Head to indulge in speculation on the structure of the thalamus and nature of cutaneous innervation with unfortunate results.

At the outset Head decided to investigate sensation from the physiological aspect, but the only method available to him was the study of the effects of various stimuli on human observers, including himself: there was no known way of analysing the events which take place between stimulation of the receptive area and the awakening of sensory experience. The resultant dependence on detailed introspective observations and repeated examination of patients with nervous lesions at various sites, usually clinically determined, must be accounted the reason for some errors in

[1]Page numbers refer to "Studies in Neurology."

Head and Rivers at work in Rivers's rooms at St. John's College, Cambridge.

deduction. Head believed that "introspection could be made fruitful by the experiences of a trained observer" (p. 226), and while this is true, the method has drawbacks which will become apparent.

Against this background of Jacksonian and evolutionary theory Head developed his ideas on the organization of the afferent nervous system, using sensory testing as his only weapon. It is peculiarly difficult to summarize the mass of clinical observations and speculative theory contained in the 862 pages of "Studies in Neurology" within the compass of one short paper. Close inspection of this classic work rewards the reader with startling glimpses of remarkable understanding and highly intelligent speculation on many aspects of sensory activity, though these are contained in a setting of diffuse, repetitive, argument which is sometimes outmoded by our increased anatomical and physiological knowledge. In general criticism it must be said that these volumes are not free from mutually contradictory statements; as Head develops the pattern of his general theory he tends to accept his earlier speculations as established fact; lastly, he is sometimes obscure, and it is hard to understand precisely what he means by the terms he uses to describe various aspects of nervous activity. His own words are used almost exclusively, though not always in direct quotation, in the following account of his general theory.

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## Head's General Theory of the Sensory System

### A. *The Peripheral Nervous System*

From his analysis of the results of nerve section he conceived three peripheral sensory systems, which developed at different phylogenetic periods, each system reacting differently to the mass stimuli of daily life; he thought this more likely than the development of specific independent systems out of primitive sense organs (p. 334). His three systems comprised those concerned with deep, protopathic and epicritic sensation.

(1) *Deep sensibility*.—This is concerned with the stimulus of pressure and with movements of joints, tendons and muscles. It is a sensory mechanism capable of providing the neural information out of which the patient is able to localize stimuli and appreciate joint movements. The fibres run mainly with the muscular nerves and are not destroyed by division of sensory nerves to the skin. The system is not concerned with the appreciation of stimuli to the skin, nor does it permit the discrimination of two compass points, even when widely separated.

(2) *Protopathic sensibility*.—The properties of this system may be recognized in the behaviour of the intermediate area of sensory loss after nerve section. Head believed that the nerve injury and differing rates of regeneration of fibres in the protopathic and epicritic systems enabled him to recognize these properties. He wrote, "the protopathic system is capable of responding to painful cutaneous stimuli and extremes of heat and cold. Its end-organs are grouped in points on the surface of the body sensitive to only one of these stimuli. Their response is diffuse and unaccompanied by any definite appreciation of the spot stimulated." The pain response from a protopathic area is intensely disagreeable, being more vivid and unpleasant than that evoked from normally innervated areas. Pinprick is more intolerable than in normal areas, the sensation radiates widely and is localized in remote parts. Although the sensory reaction is excessive, the strength of stimulus required to evoke it is never less, and frequently more, than that needed in normal parts. This intensification of sensations also occurs in response to more extreme thermal stimuli: the response is more vehement. The system also endows hairs with the power of reacting to painful stimulation and movement. The unit of distribution of the protopathic system is the posterior nerve root. Visceral sensation is entirely protopathic. The characteristics of the protopathic system are high threshold, long latencies, poor localization, failure to adapt and intense response to stimulation. The system regenerates rapidly if the ends of the divided nerve are sutured, in the case of his own arm Head stated that regeneration occurred in seven to ten weeks. The peculiar protopathic response is due to release of painful impressions from the control normally exercised over them by the more discriminative aspects of tactile sensibility; for in normal circumstances these impressions undergo

modification or inhibition before they reach higher centres. An organism with protopathic sensibility is capable only of defensive, stereotyped, segmental or massive response to stimulation. There is a primitive protective reaction which is impulsive rather than discriminative. The mass reflex of spinal man is an example of the protopathic motor response.

(3) *Epicritic sensibility*.—This is developed later in the ordinary scale and is concerned with cutaneous localization, discrimination of two points and recognition of the finer grades of temperature, called cool and warm. The undiscriminative responses of the protopathic nervous system are controlled and modified by the epicritic. This system is developed in response to the need for a more discriminative reply to stimulation created by the higher development of awareness. In normal circumstances there is no question of protopathic and epicritic sensation, for the defects of the protopathic are corrected by the simultaneous activity of the epicritic system. The unit of distribution of the epicritic system is the peripheral nerve. It regenerates more slowly than the protopathic, sensation beginning to return six months after nerve division and suture. The epicritic system is characterized by low threshold, short latencies, high adaptability, accurate localization and discrimination.

B. *The Grouping of Afferent Impulses in the Spinal Cord*

"The grouping of afferent impulses on their way from the periphery is probably determined by reasons of phylogenetic development. But as soon as the first intramedullary cell-system is reached, these impulses become shunted into paths along which they travel in new combinations" (p. 337). It is no longer a question of protopathic and epicritic. The opportunist grouping of the periphery gives way to an arrangement according to quality. "Impulses from the primary level which have been initiated by painful stimuli of whatever kind, are united into a single group" (p. 404). Similarly, tactile and thermal impulses from both systems recombine. When these peculiar impulses reach the spinal cord they are discharged into the secondary systems, each of which is guarded by specific receptors, reacting to one type of stimulus only. "It is as if the gallery of a concert hall were fitted with a series of resonators, each of which was tuned to a certain note. Each resonator would pick up a peculiar tone, whether it was produced by the strings, the brass, or the woodwind" (p. 405). The secondary fibres carrying impulses subserving pain and temperature cross rapidly to the opposite side. Fibres concerned with epicritic and deep sensibility pass in the posterior columns; sensory impulses underlying the recognition of passive position and movement and tactile discrimination do not cross within the limits of the spinal cord, but lesions of higher centres show that these ultimately cross and are grouped anew (p. 400). Head found it difficult to analyse the grouping of sensory fibres in the brainstem as the pathways are more closely associated

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anatomically, and his account is not easy to follow. He states clearly, however, that the fibres concerned with postural sensibility and spatial discrimination part company at the posterior column nuclei.

C. *The Thalamus*

The thalamus is the site of termination of all secondary sensory pathways. It contains a mass of grey matter, the essential organ of the thalamus, which is the centre for certain fundamental elements of sensation. The essential organ is complementary to the cerebral cortex and exercises different functions in the production of sensation. The lateral part of the thalamus is the organ through which the cortex influences the essential thalamic centre. Excessive response to afferent stimuli is due to removal of cortical control, but cortical lesions produce no thalamic over-response since the corticothalamic fibres come from many areas and cannot be removed by partial destruction of the cerebral hemispheres. The only certain method of producing thalamic release is to destroy the lateral nucleus. The essential activity of the thalamus consists of an excessive response to affective stimuli; there is an actual overloading of sensation. The excessive response is evoked by both pleasurable and painful stimuli. The thalamic centre is mainly concerned with the affective side of sensation, it refuses to react to impulses underlying purely discriminative activity. Sensations enter consciousness at the thalamic level.

D. *Nature of Sensory Activity of the Cerebral Cortex*

The cortex is the second terminal centre of the afferent system. "The function of the cortex in sensation is to endow it with special relationships, with the power of responding in a graduated manner to stimuli of different intensities, and with those qualities by which we recognize the similarity or difference of objects brought into contact with the body" (p. 728). The cortex is thus concerned with spatial and tactile discrimination, with dimensional relationships, and with the accuracy of response to tactile and thermal stimuli. It is also concerned with attention and the relation of stimuli to past experience. The disturbances of sensation caused by cortical lesions are manifested in defective attention and discrimination. The primary centres of the cortex cannot receive components which underlie feeling tone.

*General Conclusions*

Head states his general conclusions in Chapter 9 of the paper on Sensation and the Cerebral Cortex (p. 741 *et seq.*). He wrote, "We have laid down that the superficial structures of the body are innervated by two mechanisms, one of which we say exhibits more primitive characters than the other. Removal of epicritic sensibility exposes the activity of the protopathic system in its full nakedness. In the same way, when removal of the influence of the cortex cerebri sets free the optic thalamus from

control, sensation assumes an overwhelmingly thalamic character. In each case a lower, more primitive organization is permanently kept under control by the activity of a higher afferent system (p. 743). . . . Pain is the oldest defensive reaction and potentially painful stimuli are the basis of all primitive reflexes. It is, therefore, of importance for higher development, that these impulses should be rendered less effective in favour of those impressions which can lead to a more discriminative response. But although they are controlled and even abolished, the mechanism underlying the production of pain must remain in full physiological activity ready to play its part . . . in the defence of the body against noxious influences. The functions of the nervous system are not a palimpsest . . . The more primitive activities have been profoundly modified by the advent of the new centres, which utilize some of the faculties originally possessed by the older mechanism. In many cases the higher function could not be exercised without the existence of those lower powers which it dominates and controls . . . The part played by the sensory cortex is based upon the activities of the optic thalamus; without crude sensations of heat and cold, discrimination would be impossible, and the finer thermal relations could not be appreciated (p. 745). Between the impact of a physical stimulus on the peripheral end-organs of the nervous system, and the simplest changes it evokes in consciousness lie the various phases of physiological activity. The diverse effects produced on the living organism by a stimulus are sorted, combined and inhibited in their passage through the central nervous system, and the ultimate results finally act upon their appropriate centres. . . . By the time afferent impulses reach one of those centres, where they can form the underlying basis of sensation they have been profoundly modified. Such integration is the essential task of the central nervous system (p. 745). This process is repeated throughout the nervous system until the final products of integration come to act on two terminal physiological centres, the cortex and optic thalamus (p. 746). . . . The simplest sensory act is the result, not only of prolonged qualitative integration, but of a constant struggle for functional dominance. On the higher physiological planes impulses which are precluded from exciting sensation are not wiped out; they may produce a profound and manifest effect, although they cannot excite consciousness" (p. 761). In the appendix (p. 831) he concluded, "Our conception of the mechanism of somatic sensibility is fundamentally opposed to all previous psychological and physiological teaching. . . . There are no basic physiological activities corresponding to 'primary sensations.' The afferent impressions produced by the action of an external stimulus are highly complex, and are subjected to the integrative action of the central nervous system before they can become fitted to subserve sensation. Qualities such as pain, heat and cold, are abstracted from the psychical response and spoken of as 'primary sensations'; but they have no exact physiological equivalent in the vital reactions of the periphera

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mechanism. A 'primary sensation' is an abstraction. Afferent physiological processes are most complex at their origin; they become continuously more specific and simpler as they are subjected to the modifying influence of the central nervous system."

*Discussion*

An examination of the protocols in Studies in Neurology and, more particularly, of the notes made during the investigation of the "Case of H. H. and His Arm," cannot fail to convince the reader of the great care with which all Head's practical work was carried out. The methods of sensory examination which he developed in association with Holmes form a landmark in neurological history. Most of his observations on the effects of lesions of the sensory pathways are in complete accord with those of earlier and later workers. He provided the first description of the peculiar sensory changes which occur in the areas of intermediate sensory loss in persons with lesions of peripheral nerves. His account of what is still called the protopathic response to painful stimuli and hair movement has been amply confirmed. Whilst Head might have appreciated these compliments paid to his careful methods and lasting clinical contributions there can be little doubt that he would have wished to be judged on the basis of his theories on the organization of the afferent nervous system. It is impossible to achieve an adequate criticism of his concepts in a short space, partly by reason of the mass of material he presented, and partly because of the proliferation of his ideas relating to many aspects of sensation. His constant insistence on interpreting his theories in terms of evolutionary and Jacksonian thought and his penchant for inventing anatomical structures to fulfil his ideas have tended to obscure much that is valuable in his work; they have also rendered him an easy object for criticism. Reference has already been made to the contradictory statements which are to be found in Studies in Neurology. His examples chosen to illustrate general ideas were not always fortunate. The picture he drew of the protopathic animal provided a sitting target for Walshe's shafts (1942). His comparison of the intramedullary receptors in the spinal cord with resonators in a concert hall betrays a strange confusion in his mind between tonality and timbre.

Walshe (1942) examined Head's work in his Critical Review of The Anatomy and Physiology of Cutaneous Sensation. He concluded that Head's theory of the morphological constitution of the afferent nervous system was invalid, and that his general theory was fatally handicapped by the attempted inclusion in it of a fallacious notion of the structure of the peripheral mechanisms of sensibility. Walshe also found Jacksonian and evolutionary theory defective in the way Head used them to reach his generalization. On the purely observational side there were important differences between Head's findings in the human experiment in nerve division and those of Trotter and Davies (1909, 1913) and Boring (1916),

who used similar techniques, and Walshe has discussed these in detail. In part the contradictory results were due to different methods of examination, but this cannot be the whole explanation. The personalities of the observers afford a further partial explanation of the discrepancies. It is clear from his own reports that Head was acutely sensitive to painful and pleasurable stimuli, and the worker using introspective sensory techniques of examination enters the dangerous realm of tactile æsthetics. The dissimilar terms used by Head and Trotter to describe their experiences afford insight into their temperaments. Indeed, the preparation of this communication, and personal experience in the examination of a denervated area of skin, have convinced me that sensation is best investigated by using naïve observers in carefully planned experiments. Furthermore, the examiner's ideas may be communicated to a patient under investigation. There is a suspicion that this may have been the case in some of Head's patients with thalamic lesions, for their sensory experiences were unique, and it may well be that he set the scene, or created the situation, in which these exceptional events occurred. The contrast between Head and Trotter is seen again in the theories they expounded to explain their findings at personal nerve section. Trotter produced a modest theory of defective nerve insulation, which was reasonable in the light of existing knowledge, though it is no longer acceptable. Head, on the other hand, developed an imaginative, general theory. It must be admitted at once that the discrepant findings of Trotter and Davies, and of Boring, are in accord with what we now know of the pattern of cutaneous innervation, whereas those of Head are not. He was unaware of the pattern of overlap in denervated areas, of the way in which fibres grow in from adjacent areas, and this was a fatal handicap to his speculations regarding cutaneous innervation when he was also dealing with the complication of nerve regeneration. On the other hand, his speculations regarding the organization of the thalamus may prove to be less wide of the mark than has been supposed.

## Head's Views on the Basis of Sensory Discrimination and Duality in the Afferent System in the Light of Recent Research

While many of Walshe's (1942) strictures are still applicable to Head's general theory, the work of the past decade on the anatomy and physiology of the afferent system has altered the climate of opinion regarding some of his ideas, in particular his conception of the modification of nerve impulses, and his belief in a dual afferent system. Rose and Mountcastle (1959) have written that unqualified rejection of Head's theories is premature.

In the years since Head completed his work on sensation physiologists have investigated the responses of the nervous system to various stimuli, and in this field the method of unit analysis introduced by Adrian has been

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particularly rewarding. The great majority of these studies has been carried out in animals, often under anæsthesia; besides the complications which this approach introduces, there are other difficulties in interpretation, as Rose and Mountcastle (1959) have stated. The method of investigation does not allow an interpretation of sensations in terms of neural events, though Hensel and Boman's (1960) work in humans constitutes a notable exception. Every activity evoked in the nervous system by peripheral stimulation is not necessarily concerned with the arousal of sensation; and stimuli cannot always be related to receptors, but rather to the tissues containing them.

The anatomical studies made by Weddell and his colleagues, and others, have confirmed early reports that Von Frey's concept of types of end-organ is incorrect; so, for that matter, is Head's idea of a double set of receptors for each modality. Examination of hairy human skin, which covers more than 90 per cent of the body surface, has shown that there are two types of nerve fibre termination, free nerve endings and hair follicle endings. In non-hairy human skin the terminations are again of two types, free nerve endings and compact aggregations of axonal and filamentous entanglements, of which the Meissner corpuscles in the palm of the hand are an example. Other morphological features such as end-bulbs, are attributed to abortive attempts at regeneration (Weddell *et al.*, 1959). It seems clear that stimulation of structurally similar nerve terminations provides the neural bases from which different modes of sensation are experienced and distinguished. Anatomically identical nerve terminals must be attached to fibres of different size.

Turning to the physiological aspects of cutaneous sensation, it is necessary at the outset to define modality specificity; by this term we mean that a sensory receptor has a low threshold to adequate or reasonable stimulation of one kind, and the threshold is raised to other kinds of stimulation. No fibres are modality-specific in the extreme sense of the term, for they will all respond to abnormal stimuli, such as electrical or chemical stimulation. Non-specificity for stimulation does not exclude specificity for sensation. The subject of polyvalent fibres has been explored in animals by many workers, and there is ample evidence that numerous fibres respond to both mechanical and thermal stimuli; the mechano-receptor A fibres possessing this property react only to considerable temperature gradients, that is to say they are differentially sensitive. Hensel and Boman (1960) have attacked the problem in human subjects, and this has allowed them to determine the specific sensation evoked by excitation of a receptor, and to record the receptor response. They state that human skin contains a great number of highly specific A fibres which show no response to cooling. It appeared that very few, and perhaps only one, impulses were sufficient to produce conscious, localized

sensation. They also discovered certain fibres responding to mechanical stimulation and cooling, although thermal sensations were only aroused if a considerable stream of impulses was evoked.

The attempts made to link modality with fibre size may be said to have failed in view of the discovery of specific tactile and thermo-receptors among C fibres. Indeed, specific touch receptors have been found throughout the whole range of afferent fibres, from the largest myelinated to the smallest C fibres: specific thermo-receptors have been identified in the medium and smaller A fibres and in the C group (Iggo, 1958, 1959; Zotterman, 1959, 1961). Specific pain fibres have not yet been demonstrated, and if these fibres exist they should lie in the A delta and C range; the large diameter fibres can be safely excluded. Completion of the analysis of C fibres may resolve this point, but so far investigation has shown that the group covers the whole range of cutaneous afferents; some fibres are highly specific and sensitive to one form of stimulation, but there is a wide range of sensitivity and thresholds; the extremes can be classified (Iggo, 1961). These experimental findings point to the existence of many specific receptors, besides differentially sensitive and bi-modal fibres, subserving cutaneous sensory modalities. Impulses are conducted in various temporal and spatial patterns to the spinal cord. Only the largest diameter fibres pass via the posterior columns to the posterior column nuclei in the brainstem, but there is evidence that fibres of all sizes terminate on cells in the posterior horn, and recent findings indicate that impulses are subject to modification at this level. Wall (Wall, 1960; Wall and Cronly-Dillon, 1960) studied the problem of central modality analysis by micro-electrode investigation of cells in the posterior horn of the spinal cord in cats, and his cautiously stated conclusions are of great interest. He set out to examine the nature of convergence of peripheral fibres on nerve cells. Selecting only those cells which responded to light touch, he found them distributed in a laminar, topographical arrangement in the dorsal part of the posterior horn. The receptor area to light touch was well defined, averaging 63 by 32 mm. The cells were activated by all stimuli to which the animal is known to respond, including thermal, mechanical, nocuous and itch-producing stimuli. Wall suggests that fibres of all diameters converge on these nerve cells, so that they respond to all modalities of skin sensation, but differences in the pattern of discharge depend on the nature of the stimulation. The destination of the axons of these cells is unknown; it is uncertain whether they are concerned in spinal, cerebellar or somatosensory arcs; nevertheless, the idea that modality may be encoded as a temporal pattern of impulses in common-carrier cells is of obvious importance.

These anatomical and physiological findings indicate the inadequacy of the view that discrimination of cutaneous sensations depends on differ-

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entiation into four modalities at the peripheral receptors, whence information is conducted directly to the brain. Head's picture of modification, integration and inhibition of sensory impulses in their passage through the nervous system is in remarkable accordance with the results of this recent work.

It may be said of Head's theory of a dual cutaneous afferent system that the specific mechano- and thermo-receptors manifest in a general way the properties he attributed to the epicritic system. No group of fibres has yet been found to fulfil the requirements of a protopathic system at the peripheral level. The phenomena which Head ascribed to the activity of this system, as the result of his own experiences in the Human Experiment in Nerve Division, are adequately explained on the basis of reduction in the pattern of cutaneous innervation. However, a possible physical basis for the protopathic reaction, as distinct from the protopathic system, exists at higher levels.

*Duality in the Somato-sensory System*

The range of responses in the central sensory pathways which can be attributed to electrical and physiological peripheral stimulation has been investigated in animals by a number of physiologists (e.g. Gaze and Gordon, 1954, 1955; Landgren, 1957*a*, *b*, 1959; Albe-Fessard and Kruger, 1959). Mountcastle and his colleagues have published a series of papers dealing with the functional contribution of the lemniscal and spinothalamic systems. As their findings are of particular interest in relation to Head's theories, they will be considered in some detail. Working largely with cats they studied the response to peripheral stimulation of single nerve cells in the ventro-basal complex (Rose and Mountcastle, 1959) and posterior nuclear group of the thalamus (Poggio and Mountcastle, 1960). Cortical cells in the first and second somatic sensory areas were included in the survey.

A. *The Lemniscal System*

This system deals with tactile and kinæsthetic impulses, which are conducted by large myelinated fibres via peripheral nerves and posterior columns to the cuneate and gracile nuclei in the medulla. Here the second order afferents arise and pass after decussation to the ventro-basal complex of the thalamus, whence nerve cells project to the primary somatic sensory area in the post-central cortex. Using tactile and kinæsthetic stimuli, Mountcastle found that the opposite side of the body is represented topographically in the ventro-basal complex. The image of the body form is distorted, the volume representation of a part being related to the density of innervation. Although afferent nerve volleys produce responses in the ipsilateral thalamus, physiological stimuli do not evoke ipsilateral

activity. Each thalamic cell is related to a specific and unchanging receptive field on the opposite side of the body and the relation between periphery and thalamic nucleus is said to be one of point to point. The cells are modality-specific; they respond to mechanical stimulation of the skin or deep tissues, or to joint rotation. The response patterns of the cells have been studied in detail, and Poggio and Mountcastle (1960) conclude that the lemniscal system "is tuned for action in rapid tempo, and capable of presenting at the cortical level patterns of neural activity which are most sensitively determined by the temporal and spatial properties of the peripheral stimuli." Investigation of the cortical cells at the termination of the lemniscal system has shown that they share similar properties of contralateral representation, receptive fields, modality specificity and response patterns with the cells of the ventro-basal complex. Afferent inhibition has been demonstrated in neighbouring cells at the cortical level.

B. *The Spinothalamic* (*Anterolateral*) *System*

The spinothalamic tract takes origin from cells in the posterior horn of the spinal cord and conducts impulses associated with the evocation of pain, heat, cold and sexual sensations. Little is known of the precise properties of the fibres which make up the tract, but presumably some must be modality-specific as the pathway conducts impulses associated with thermal sensibility; it also contains a small number of lemniscal fibres. Some workers state that myelinated and unmyelinated fibres terminate in the reticular formation of the brainstem, others passing direct to the intralaminar and centro-median thalamic nuclei. In the cat some fibres end in the ventrobasal complex of the thalamus, and in man a higher proportion terminate in this way, but the sensory component which accounts for this increase is not known, nor the modality served. Part of the cat's spinothalamic tract terminates in the posterior nuclear group of the thalamus, a broad cell band lying behind the ventral and lateral nuclei, adjacent to the geniculate bodies and difficult to analyse or subdivide. This area is cortically dependent and projects partly to the secondary somatic sensory cortex. Single unit studies have been more difficult to achieve in this area, but Mountcastle and his colleagues describe the following results. The cells are fired by stimulation of a wide, and sometimes bilateral, receptive field; indeed, there is a good deal of bilateral representation. 40 per cent of cells responding to somatic stimulation are activated by light touch, but these mechano-receptors are not place-specific, and there is no orderly projection of body form. The cells are not modality-specific, for they may also be driven by auditory and vibratory stimuli; others respond to noxious stimuli applied outside their receptive field. 60 per cent of all cells studied responded solely to noxious stimuli, such as pinching and pin-prick. No cells examined responded to joint rotation. The anterior



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part of the posterior nuclear group includes the secondary somatic cortex in its projection area. The response properties of the cells are different from those of the lemniscal system, including prolonged after-discharge to noxious stimuli and, in some instances, longer latencies. Investigation of single cells in the secondary somatic cortex has shown that some have functional characteristics of the cells of the lemniscal system; but others have properties similar to those of the cells in the posterior nuclear group, and Mountcastle and Powell (1959) found cells of this type in the post-central gyrus of the monkey. It is therefore suggested that the first and second somatic areas are mainly concerned with the functional activity of the lemniscal and spinothalamic systems respectively, but neither exclusively so.

A comparison of the functions of these two systems suggests that in the animals studied they contribute to final sensory experience in very different ways. The lemniscal system is a finely tuned, rapidly conducting, highly adaptive, mode- and place-specific apparatus; its properties indicate that it provides the basis for the discriminative and localizing functions of the nervous system. On the other hand, the spinothalamic system is characterized by wide receptive fields, lack of modality-specificity and slow adaptation. A sensory apparatus possessing these qualities would be likely to impart little information about the site of a stimulus or its duration, but it might provide considerable evidence of noxious stimulation. Poggio and Mountcastle (1960) offer the following generalization, "One can consider the ventro-basal complex and the geniculate bodies, together with their essential cortical projection areas as the essential cores of the somatic, visual and auditory systems. Surrounding them at both thalamic and cortical levels, and fusing between them, are areas which are less specific with regard to local sign and modality served, in which complex interactions occur, and which are thought to subserve sensory integrative actions." These findings are of obvious significance in relation to Head's concept of a dual afferent system, though admittedly he envisaged this operating at the peripheral level; his speculations regarding the properties of such a system show signs of fulfilment. Furthermore, his theory of cortical and thalamic organization and interaction receives experimental support; on an occasion such as this one may speculate and suggest that the behaviour of the cells in the posterior nuclear group approximates to that of Head's imagined essential organ of the thalamus.

## Conclusion

This is a difficult time to assess the ultimate value of Head's contribution to the subject of sensation, for knowledge is increasing rapidly. Twenty years ago it appeared that he would be remembered as a speculator whose theories had been outmoded by scientific advance: the evidence on which

he based his views had been largely discredited, and his philosophical extension of his ideas had been effectively demolished. The criticism of these aspects of his work are still valid. It is therefore remarkable that his general theory should have received so much favourable comment during recent years.

Walshe (1942) has acknowledged that Head's contributions remain a most impressive body of observation that must have permanent value, and that his work has enriched neurology. To this tribute we may add the submission that, shorn of its evolutionary content and speculative detail, his concept of the organization of the afferent nervous system approximates more closely to our own than those of his contemporaries, and still provides a stimulus to workers in the field of sensation. Surely he could have asked no more for this, his centenary, year.

I am grateful to Dr. E. H. Lambert, The Mayo Clinic, Rochester, Ma., who drew my attention to Head's account of the effects of positive acceleration on aviators. The photograph of Head and Rivers is reproduced by kind permission of Professor O. L. Zangwill.

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# HEAD'S CONTRIBUTION TO APHASIA[1]

BY

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HENRY HEAD first became interested in aphasia while he was investigating sensory effects of cortical lesions, in about 1910. He became aware that the responses given by the testee often betray a defect of communication as well as perception. A percentage of sensory stimuli might be missed altogether, and increasing the strength of the stimulus does not necessarily raise the patient's accuracy in scoring. One particular aphasic subject when tested with compasses for tactile discrimination could not proclaim whether he was being touched by one point or by two: neither could he indicate in writing. But when Head put before him a sheet of paper upon which were printed the numerals *one* and *two*, the patient could promptly touch the appropriate symbol. Such observations caused Head to doubt the validity of current ideas about aphasia, and sent him to his library. The classical writers did not satisfy his doubts or explain his clinical findings and it became obvious to him that new tests were needed. Most physicians and surgeons, he said, unfortunately were ill-prepared to deal with the opportunities afforded by cases of aphasia. Time and energy for long-continued examination were lacking, and the methods in general use were too crude to provide satisfactory results. But among the many papers by Hughlings Jackson scattered among obscure and out-of-date journals, he found the key for which he was searching. Jackson had interpreted the problems of language-disorder along lines which appealed to him forcibly, even though they had made but little impress upon contemporary neurology. In 1914 Head also discovered Pick's monograph "Die agrammatischen Störungen" which though wordy and muddled—voluminous, he called it—was almost as stimulating as Jackson's writings.

Head's wartime role as Consultant to the Empire Hospital for Officers brought him in touch with a number of healthy, intelligent, but brain-injured young men showing a diversity of disorders in expression. This opportunity stimulated and facilitated his plans, and became the final factor

[1]Paper read at the Henry Head Centenary Celebrations at the London Hospital, August 31, 1961.

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determining his ultimate research. Head's intellectual make-up was peculiarly fitted for this task. His natural gusto drove him to grasp one of the thorniest problems in neurology: his obsessional traits ensured a scrupulous and minute clinical scrutiny: his erudition embraced the continental literature: his critical bent showed him the weaknesses of accepted dogma as well as the strength of Jackson's ideas. Finally his originality, disciplined by philosophy, led him to novel and exciting conceptions in aphasiology.

Head's first foray into this controversial subject consisted in a compilation of the most important of the relevant papers by Hughlings Jackson. In 1915 he reprinted these in a single issue of BRAIN. Though only 58 years of age, he now resigned his hospital appointment as though dedicating himself to what was to be his finest hour in neurology.

In 1920, Head delivered the Linacre and then the Hughlings Jackson Lectures, both of which dealt with the topic of aphasia. Here he ventilated the ideas which had been maturing over the previous five years. Here we can find Head's criticisms of orthodox views, his personal aphasiological *credo*, his technique of examination, his revision of terminologies, and the replacement of older classifications by a new psycholinguistic grouping. Ordinarily no discussion follows the Jackson Lecture, but five weeks later a special meeting of the Section of Neurology was held, in which some of his colleagues ventured their objections and observations. Collier was clever and constructive; Wilson was very Wilsonian; Purves Stewart and Barnes were not impressive, while Herbert Parsons was obscure and somewhat irrelevant.

In 1923 Head gave his Cavendish Lecture upon speech and cerebral localization. The same year, a contribution to von Monakow's *Festschrift* dealt with a case of acute verbal aphasia followed through the various degrees of recovery. Head's final exposition appeared in 1926 when he issued his two-volume monograph entitled "Aphasia and Kindred Disorders of Speech." A re-statement of his personal attitudes was preceded by an intriguing survey of the history of aphasia-research. Head was critical of most authors, especially those whom he dismissed as diagram-makers. Modified praise was accorded to Pierre Marie "the iconoclast," to Kussmaul, and to Van Woerkom, while he bestowed whole-hearted approval upon only Jackson, Pick and Goldstein.

What then may we regard as Henry Head's personal contribution to the problem of disordered language?

Like Jackson, Head emphasized that speech is no more a localizable faculty than is eating. Brain-disease, however circumscribed, can never affect speech and speech only. The clinical picture of an aphasia often depends more upon the acuteness and severity of the onset of the lesion, than upon its extensity.

Any organic process which gravely impairs speech, also disturbs other functions not usually classed with the use of language; it also spares and leaves unaffected much that undoubtedly belongs to speech. The more carefully the patient is examined the less certainly does his disorder correspond with any preconceived category.

Gross injury to one half of the brain can disturb the power of speaking, reading and writing, without producing any severe loss of intellectual capacity. We have no right to be satisfied with the statement that the patient cannot speak, read or write: it is our business to discover the conditions under which he can or cannot perform any of these acts. Throughout his earlier papers Head repeatedly used the phrase "words, numbers and pictures" to give concreteness to his ideas and to avoid dangerous generalizations. Over and over again he inveighed against the use of the terms "aphasia," "amnesia," "alexia," "agraphia," "apraxia" and "agnosia." He reluctantly made use of "aphasia" as a shortened indicative expression which saved detailed description. Internal speech plays an essential part in other acts besides writing and speaking, and hence these acts should be specifically examined in patients with aphasia.

An aphasiac's performance is inconsistent. Therefore it is necessary when examining him to present the same task two or three times, and in several different ways. The procedures should be carried out in an environment of quiet, and every remark or aside on the part of patient or examiner should be recorded. The speed of performance should be noted also.

Head then proceeded to draw up a battery of tests which was a great advance upon the current haphazard methods of investigation, and also upon the techniques suggested by Rieger and by Pierre Marie. Some of the tests were later criticized as not pertaining strictly to linguistic ability, but to Head they were indices of the state of the patient's inner speech, and were consequently relevant and important.

After unilateral lesions, not every modality of language is necessarily disturbed in any one case. The more acute and severe the lesion, the graver and more extensive will be the disorder it produces. Slighter and more localized lesions may lead clinically to dissociated manifestations, or "types" of aphasia. There is an analogy with the sensory cortex where complete loss of all forms of discrimination may occur, or, partial disturbances which involve one aspect more than another.

These dissociated forms of speech-loss are not the primary elements out of which speech has been evolved: they are not to be described in terms of reading, writing and speaking. Neither do they stem from loss of motor or sensory power, or from destruction of images; or from a diminution of general intellectual capacity. They are none of these things. They are the product of the breaking-up of one aspect of psychical activity; analogous,

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but on a still higher level with the sensory dissociations following a lesion of the post-central cortex.

In every one of these dissociated forms there is both a formative and an emissive aspect, and both of these are always affected.

Head thereupon advanced a new classification of verbal, nominal, syntactical and semantic types. He did not define these, but he described them at length. It is not necessary to reproduce his text but merely to state that in *verbal aphasia*, words are evoked with difficulty and tend to be abnormal in structure. *Nominal aphasia* leads to defective use and understanding of words as names or indicators. With *syntactical aphasia* the internal balance of a word as an orderly rhythmic expression is disturbed, and jargon results. *Semantic aphasia* interferes with the capacity to comprehend and retain the general significance of a word as part of a complete act of language.

Perhaps these descriptions are short of crystal clear, but the phraseology is Head's and Head never afforded us any simpler interpretation of his ideas.

Head had to admit that these forms of dissociation did not as a rule appear in isolated form, and that in a few cases only did the actual loss in function remain confined to any one of these clinical types. As he himself confessed ". . . these designations are empirical; they have no value as definitions and must not be employed to limit the extent of that loss of function to which they are assigned. Each group includes disorders of wider extent than those comprised under the name by which it is known."

In his Cavendish Lecture Head tried to correlate his types of aphasia with the anatomical site of the brain-lesion. He adopted a careful and commendable method of reconstructing the lesion upon the basis of anatomical casts. The act of speech varies, he said, and assumes different forms according to the situation of the injury, just as a man's gait varies according to whether he has hurt his heel or his toe. Lesions of the lower part of the pre- and post-central convolutions, and the parts beneath them, lead to difficulty in finding verbal forms. Syntactical defects are associated with disease of the upper convolutions of the temporal lobe, and semantic types of aphasia with lesions around the supramarginal gyrus. Nominal aphasia though clinically distinctive, had a less firmly established morphological basis, but it seemed to centre around the angular gyrus.

Head never seemed quite happy with these efforts at localization. He said that his attempts to explain how a lesion in a certain part of the brain came to be associated with defects of symbolic formulation and expression were purely hypothetical suggestions which did not form an inherent part of his general thesis.

Anticipating Luria's conception of a loss of the regulating, directive, or pragmatic functions of speech, Head described how an aphasiac might succeed in reading a printed request but without carrying out the com-

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mand. What then, he asked, really is the function which is upset in aphasia?

Head observed that aphasiacs are able to carry out any operation which does not demand formulation of symbols. When an aphasiac cannot name an article, but can describe its use by resort to a periphrasis, he is expressing a lower grade of symbolic recognition. "Each particular variety of aphasia represents the response of the organism under the changed condition produced by physiological defects." This dictum of Head's is strikingly akin to the principle enunciated forcefully by Goldstein, and it is difficult to determine which author merits the priority. All forms of immediate perception are intact so long as no symbols intervene; but all acts of symbolic thinking and expression are liable to be affected, more or less, in cases of disordered language. This corresponds with Hughlings Jackson's notion of the formation of propositions.

It was with the greatest reluctance that Head ventured to change Jackson's nomenclature, but he believed that under the uncouth term "propositionizing" was included what was in his mind when he referred to "symbolic thinking." The question of what constituted a proposition was so disputable that Head thought it better to avoid a term which was so liable to be misunderstood and to lead to controversy. He doubted moreover whether the term was strictly accurate even in the Jacksonian usage.

Head therefore suggested that the function affected in pathological conditions might be called "symbolic thinking and expression." Deferring to subsequent objectors, Head afterwards changed this phrase to "symbolic *formulation* and expression."

In no place did Head explicitly use these words as a definition either of language or of speech, though subsequent writers would often assume that such was Head's intention. Head's explicit use of this phrase was to indicate the fundamental mechanism which was impaired in cases of aphasia.

Concerning the mentation of aphasiacs Head asserted that it is not the "general intellectual capacity" which is disturbed, but the mechanism by which certain aspects of mental activity are brought into play. Behaviour is affected in a specific manner; an action can be carried out in one way but not another. The more concrete is lower in the hierarchy of mental processes than the general and the abstract. The higher the propositional value of the mental act, the greater difficulty will it present. Somewhere on the ascending scale of difficulty the aphasiac will break down.

Regarding the ability to comprehend, Head pointed out that much of what is said by an educated person is incomprehensible to one of lowlier grade, who accepts just enough to get by, hoping it will suffice. An aphasiac of high pre-morbid intellectual stature may be the same. Recognizing his defects he jumps to conclusions without the usual logical steps. He no longer possesses the normal means of complete understanding. His replies are sometimes right and sometimes wrong. Moreover, he may be

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driven to adopt childish methods like spelling out words letter by letter, or reckoning on his fingers.

"In so far as these (symbolic) processes are necessary for the perfect exercise of mental aptitudes 'general intelligence' undoubtedly suffers. For a man who, in the course of general conversation, is unable to express his thoughts, or comprehend the full significance of words and phrases, cannot move freely in the general field of ideas . . . Moreover it must not be forgotten that the intellectual life of civilized man is so greatly dependent on speaking, reading and writing, that any restriction of these powers throws him back upon himself; he shuns company and cannot occupy himself with the newspaper or social intercourse. This inevitably leads to a diminished field of thought, and many aphasics gradually deteriorate in mental capacity. Yet closer observation shows that this 'want of intelligence' is based primarily on some distinctive defect in a definite form of behaviour."

In some of the foregoing we perhaps detect a little inconsistency in attitude on Head's part, even a trace of contradiction. But Head was like that. His thoughts ranged widely and deeply: all were committed to a paper, and self-censorship was rarely severe.

Head remarked that in some ways the manifestations of aphasia resemble the stages through which language is acquired in an individual. Thus, dissolution would seem to recapitulate evolution. But Head hastened to demonstrate the error of such an idea. The mechanism underlying speech is not a palimpsest from which an earlier and primitive text is revealed when the more recent writing is removed. The aphasiac has a mind which differs fundamentally from that of a child, even though he may react to his linguistic shortcomings in a manner resembling that adopted in childhood.

At a later stage Head introduced into his writings upon aphasia two further conceptions, namely those of "schemata" and of "vigilance." The former was a carry-over from his studies upon sensation, and Head believed that models or patterns are identifiable in speech upon which subsequent patterns can be erected. The response of an organism to a stimulus depends upon an arrangement of preceding reponses, already organized, but occurring outside of awareness. These responses are what he called "schemata." They may occur at any level of physiological response including those processes which convert thinking into speech. Head was vague upon this subject and did not elaborate these ideas. Others have since done so. This notion also ties up with Head's very speculative doctrine of vigilance. Again, Head refrained from exactly defining what he understood by this mechanism. He seems to have envisaged a sort of high-grade physiological efficiency which lies behind all types of nervous activity from the lowest to the highest. In the case of the latter, Head's "vigilance" is very reminiscent of the orthodox notion of

attention, which, whether it be an active or a passive process, is extremely sensitive to the effects of stress and disease. Perhaps today it would be equated with a species of high-level feed-back operation, acting as a governor or brake upon other aspects of mentation.

Throughout the 1920s Head's opinions upon aphasia were naturally criticized, for they were disturbing; but little opposition appeared in print. In the debate which followed the Jackson Lecture, it was deemed unwise to abandon the contrasting motor and sensory types of aphasia so useful in clinical diagnosis. The new classification was not received with enthusiasm especially as Head had to admit that his types rarely existed in pure form. Kinnier Wilson urged, and continued to urge, that there were expressive and receptive types of aphasia, and that the former could be equated with an articulatory apraxia and the latter with an agnosia. When the opportunity presented, in his 1926 monograph, Head protested that those defects of language exemplified by both imperception and by apraxia were of different order from those in aphasia. Terms like "verbal apraxia" and "agnosia" were but descriptive of certain forms of abnormal behaviour. "Used in any other sense they belong to that deceptive class of clinical terms which, although they explain nothing, produce a fictitious feeling that an absolute classification of the phenomena has been attained."

In 1926 Professor Bartlett wrote a full-dress review of Head's monograph, but it reads far more like an appraisal than a critique. This is not surprising, for Head had been in intimate touch with Bartlett upon whom he had often relied for counsel and encouragement. Bartlett's main doubt was directed towards Head's conception of "vigilance," while rating the most original and the most profoundly important aspect to be Head's doctrine and treatment of "schemata."

Forty years have now passed since Head first opened the topic of aphasia. How do his teachings stand up to present-day attitudes? What of lasting value has resulted from his contribution? Without question, Head's intervention into aphasiology has been masterly and epochal. Much of what we believe and teach today we owe to Head, possibly without realizing the magnitude of our indebtedness.

Like all other researchers, Head had to rely upon his quick ear and conscientious techniques for detecting the fragments of speech emitted by his patients. He had note of the advantages which linguists command nowadays of audible and visible methods of recording. Despite these handicaps he explored the mysterious terrain of aphasia more deeply than anyone since Jackson. Not only did he link static neurological attitudes with the dynamism of psychology—others had done this before—but he was one of the first to apply the lessons of linguistics. Others have since followed, realizing that the future of aphasiology lies in the application of

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a study of language itself. Linguistics too must certainly concern itself with language in all its aspects, including language in its dissolution and its drift, as Sapir well said.

Head's judgment of earlier workers in the field of aphasia must stand today before a higher court. Most of us would probably agree with the majority of his evaluations even though Head surely underestimated Trousseau. He also probably over-praised Pick perhaps feeling warmly towards his fellow student at the University of Prague. Oddly enough Head ignored the important work upon aphasia made by Freud, by Bergson, and by Isserlin. But in his "historical retrospect" Head frankly confessed himself to be prejudiced, and he admitted that he had selected only certain epochs and men, as representing some definite aspect of thought.

What is today's assessment of Head's battery of serial tests? That they constitute a great advance over traditional technique is undeniable. It is no serious criticism that they are now but rarely applied. They were time-consuming and somewhat repetitive. They had the merits of being fairly rigid, and therefore suitable as a framework for the study of most aspects of disordered language. But this in itself may prove a weakness, and serial testing is apt to end in a stultifying factor-analysis with all its demerits. Head's battery of tests did not allow sufficiently for the extra-ordinary case of aphasia: the illiterate, the writer, the orator, the polyglot, the artist, the musician, and the patient of exceptional ability. Indeed it has been stated that Head obtained some of his most revealing data when he supplemented his formal tests with special *ad hoc* procedures. Head's hand-eye-ear test has come in for special criticism. Kinnier Wilson objected that it was a non-verbal manœuvre which really explored a state of "eupraxia." Head countered by asserting that an inner verbalization is very much entailed, whereby such concepts take part as "behind" "in front" "right" and "left." Later work, however, as by Quadfasel, Gordon, Fox, and others has indicated that the imitative movements concerned in this particular test do not necessarily demand a silent verbal formulation.

One particular defect of Head's battery was that, like so many other aphasiologists, he fell into the error of making no control studies. The unwisdom of this neglect is demonstrated when Pearson, Alpers and Weisenburg submitted a group of normal college students to Head's battery of tests, and found that a significant percentage scored badly.

Head's use of the phrase "symbolic formulation and expression" was an interesting and worth-while innovation. Already it has passed out of currency, partly because nowadays we look for something shorter and more utilitarian. Head often made the mistake of not defining his terms clearly and precisely at the outset of his argument. He shrank from defining the words "speech" and "language," and indeed he used the two of them interchangeably—like some modern American linguists. The

correct employment of the term "language" would adequately cover most if not all of the non-verbal processes which Head had in mind. It would include the manipulation of symbols, as envisaged by Head, even though nowadays the use of "symbol" is regarded askance in some quarters. "Communication" is perhaps the current jargon for Head's "symbolic formulation and expression" and it is certainly crisper and more wieldy.

Head's belief in a defect of symbolic formulation and expression as the basis of aphasia, has been questioned by Goldstein, by Isserlin and by von Kuenburg, though not for the same reasons. At the present time we could most satisfactorily reconcile the various objections by resorting to some such term as "communication," or better still "language" (in the precise sense).

Then again Head's hypothesis of "vigilance" seems to have perished—from neglect rather than by defeat. "Vigilance" marked an interesting exercise in speculation, but it did not really add a great deal to our knowledge either of language or of aphasia.

With "schemata" the case is perhaps different. Originally conceived by Head in collaboration with Gordon Holmes in a different context, its place in the aphasia-story received special commendation from Bartlett. Today it has been employed by Russell Brain and it may well long survive in this particular framework.

What of Head's notorious classification of the aphasias? Here again it has virtually gone by the board. It was doomed to extinction the moment it was admitted that it covered the clinical facts no more than the traditional subdivisions it sought to replace. Head's four types could not be defined; they could not be tersely described; they could not be squeezed into a morphological mould except as a Procrustean after-thought. Weisenburg and McBride have, I submit, correctly summed up the matter: ". . . When Head's classification is compared with those which are more widely accepted at the present time, it seems superior to them in theory and inferior in practice. It is based on the right principle; that is, the differentiation of forms of language deterioration in terms descriptive of the predominant psychological changes. It is not, however, so successful a differentiation of the types of disorder as many which employ far less justifiable terms" (1935).

In the coming and the going of Head's classification we see all too clearly the continuing need for a satisfactory method of grouping the manifold clinical expressions of language-disorder.

Like Jackson, Head did not evince much interest in speech as a localizable cerebral mechanism, or in aphasia as a focal symptom. One gets the impression that he was impelled into the subject he chose for his Cavendish Lecture with some reluctance—if not indeed against his better judgement. Even more striking was his neglect of the problem of cerebral dominance as concerning speech. As Kinnier Wilson said, once we admit that speech

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is a perquisite of one half of the brain, then we have the beginnings at any rate of localization. Head seemed uninterested in this question, and, in his very detailed case-reports he did not indeed always specify the patient's handedness. Head did not even follow Jackson in assigning to language some minor role in the right cerebral hemisphere.

Finally we come to Head's *magnum opus* on "Aphasia and Kindred Disorders of Speech." Henry Head was a sick man when he compiled this work, and we can perhaps detect the uncertain touch. It is prolix and repetitive, and in places even contradictory. At times Head was ambiguous or almost evasive. The work would have been the greater had it been condensed into a single volume.

These criticisms sound harsh but I think they are just. But when they have been said, Head's monograph, in my opinion, still constitutes the finest and the most significant volume in the whole literature of aphasia.

It is a strange irony. Head achieved so much in aphasia that he is remembered today more for his failings than his accomplishments. These latter have been quietly absorbed within the *corpus* of neurology. Head's faults were the demerits of a constructive and brilliant mind. After all, as Luciani has told us, a fertile error is of more value than a sterile fact. Nor should we forget the words of Vilfredo Pareto: ". . . give me a fruitful error every time, full of seeds, bursting with its own corrections. You can keep your sterile truth for yourself."

# HENRY HEAD: THE MAN AND HIS IDEAS[1]

BY

RUSSELL BRAIN

HENRY HEAD was born on August 4, 1861, at 6, Park Road, Stoke Newington. His father was Henry Head, an insurance broker of Lloyds, third son of Jeremiah Head, late Mayor of Ipswich, and Mary Howard his wife. His mother, Hester, was the daughter of Richard Beck whose wife, Rachel, was the daughter of Samuel Lucas of Hitchin. Richard Beck was the partner of his uncle J. J. Lister in a wine business in Token-house Yard, London. This Mr. Lister was the father of Lord Lister who was thus Henry Head's cousin. Through his mother he was also related to E. V. Lucas the author. Both Head's parents came of Quaker stock and, as he said, "were the centre of a multitude of friends and relations." Later they moved to Stamford Hill, to a house which William Morris decorated for them, and Henry, after attending two day-schools, went as a weekly boarder to the Friends' School, Grove House, Tottenham, where several of his contemporaries became distinguished. There he came under the influence of a master called Ashford, whom he described as "one of the best teachers of natural science I have ever encountered. To this man," he said, "I owe the fact that I was firmly grounded in the elements of natural science at an age when boys at an ordinary school in my day were ignorant of the very existence of the subject." When he was 13 he went on to Charterhouse, which had recently moved from London to Godalming, and there again he was fortunate in coming under the influence of a science master, W. H. W. Poole, who clearly realized the exceptional abilities of his pupil, for he taught him not only biology, but the elements of physiology, and gave him private tuition in dissection and cutting microscopic sections at his house.

From Charterhouse Head went to Trinity College, Cambridge, but instead of staying at Charterhouse for the last summer term he spent some months in Germany at Halle, where he studied physiology and histology at the University and devoted some time each day to learning German. In October he went up to Cambridge where his contemporaries

[1]Paper read at the Henry Head Centenary Celebrations at the London Hospital, August 31, 1961.

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and friends included a number of men destined to become distinguished, d'Arcy Thompson, W. R. Sorley, A. N. Whitehead, William Bateson and A. G. Shipley amongst them. Michael Foster was professor of physiology, and Langley and Gaskell were lecturing.

Head said once that he could not remember the time when he did not wish to make medicine his career in life, and he mentions in this connexion the influence of his mother's cousin, Marcus Beck, who had worked as assistant to Joseph Lister at Glasgow. He describes how, when he was 8 years old, his family was involved in an epidemic of scarlet fever. When Henry had recovered he was taken for a few days to stay with the family doctor, Mr. Brett, and one morning at breakfast startled his family by pouring a little tea into a teaspoon, and heating it over a spirit lamp, carefully inspecting the result, as he had seen Mr. Brett do often during his own illness, to see if he could detect albumin in the urine.

On coming down from Cambridge, after getting a first class in both parts of the Natural Science Tripos, he decided to go abroad again. Dissatisfied with some laboratories he visited in Germany, he decided to visit Hering at Prague. He was immediately impressed by Hering and the facilities available, and Hering seems to have been impressed with Head, for he at once invited him to stay and work with him. There Head carried out his work on the physiology of respiration, and listened to Hering's account of his own researches into colour vision.

After two years in Prague Head went back to Cambridge to complete his courses in anatomy and physiology, and then joined University College Hospital, London, where he qualified in 1890. There he was house physician, and he also worked at the National Hospital, Queen Square, under Dr. Thomas Buzzard. Later he was house physician at the Victoria Park Hospital for Diseases of the Chest, and it is probable that he was attracted to that hospital by his interest in the physiology of respiration. At any rate it is possible from his early writing to trace in some detail the development of what was to be his main interest in neurology. His Cambridge M.D. thesis, "On disturbances of sensation with especial reference to the pain of visceral disease," subsequently published in *Brain* (Head, 1893) was, as he acknowledged, based upon patients seen at University College Hospital and the National Hospital. It begins with these words: "Several years ago I was led to examine the positions occupied by pain in disorders of the stomach and I soon came to the conclusion that the usual description was incomplete in several respects. . . . I then began to investigate the distribution of herpes zoster in the hope that a skin lesion which was notoriously of nervous origin might throw some light on the meaning and significance of the tender areas in visceral disease. . . . I next attempted to determine to what level of the nervous system these areas belonged, with the help of cases in which

Henry Head about 1895.

*Illustration to article by Russell Brain*

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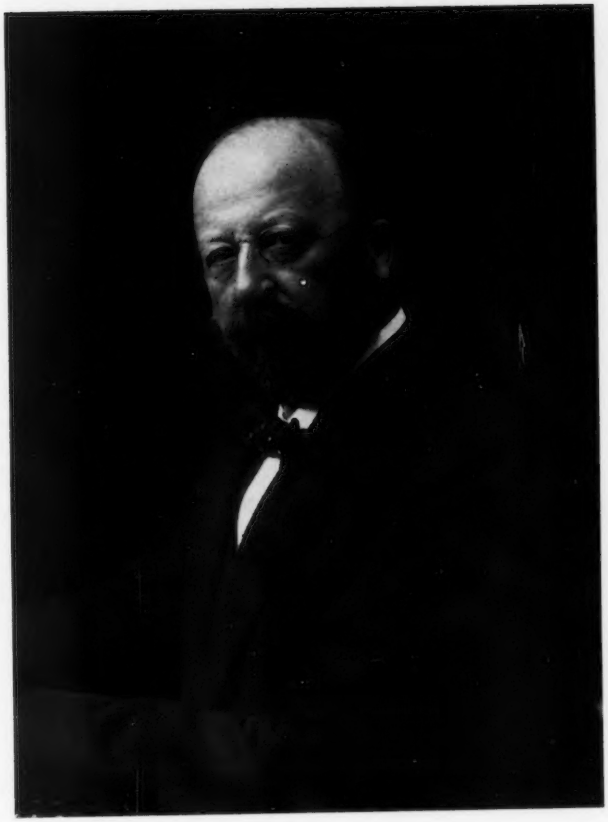
Ruth Mayhew.

*Illustration to article by Russell Brain*



Henry Head about 1914.

*Illustration to article by Russell Brain*

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gross organic lesions were present. . . . This opened up the whole question of sensation in its various forms, but in this paper I shall not do more than touch upon the relations between the distribution of the sensations of pain, of heat, of cold and of touch." His next communication on the subject of pain produced by visceral disease (Head, 1894) was based upon patients seen at the Victoria Park Hospital. Here we find him covering a wide field of medicine, and devoting considerable attention to diseases of the heart and lungs. He also studied the mental changes associated with visceral disease and made this the subject of his Goulstonian Lectures for 1901 (Head, 1901). Thus he began his medical career as a general physician with a special training in physiology, and it was visceral disease which aroused his interest in pain, and his study of pain which led him into the broader field of the neurological basis of sensation in general. And a general physician he remained to the end of his professional life.

In 1896 Head was appointed medical registrar to the London Hospital, and within four months elected assistant physician. There is a verbatim report of one of his rounds at the London Hospital in 1900. The first patient he showed had mitral stenosis, adherent pericardium and heart failure. Nearly twenty years later Dr. Donald Hunter recorded him as teaching on the difference between bronchial and cardiac asthma.

This leads me to talk of Henry Head as a teacher. Some men find teaching difficult: others are born teachers; they feel impelled to impart information to others. Head was one of those. When he was only 21 we find him addressing the Stoke Newington Mutual Instruction Society at the Friends Meeting House, Park Street, on the fertilization of plants. His devotion to teaching is well illustrated by an account of him which was given by Professor H. M. Turnbull, who wrote: "I had the good fortune when first going to the hospital to meet daily in the mornings on the steam engine underground railway Dr. Henry Head. He told me to buy Gee's little book on percussion, and kindly taught me throughout our journeys about physical signs, much to the annoyance of our fellow travellers; indeed in his characteristic keenness he spoke so loudly that as we walked to the hospital from St. Mary's station people on the other side of the wide Whitechapel Road would turn to look at us. I was greatly interested in the central nervous system when learning physiology and anatomy, and so I enjoyed greatly my three months as a clerk to him, his sessions in the out-patient department, and his wonderful demonstrations on clinical evenings. . . . He devoted a great deal of time to teaching. In his rounds of the wards his clerks read the histories and examinations they had written, and he criticized even the English. He did not confine himself to nervous diseases, but took more pains than any other physician for whom I clerked to teach us physical signs and



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how to examine patients of all kinds. He was a little too anxious to get exactly correct results when demonstrating to students; thus when he was mapping out areas of anæsthesia or hyperæsthesia the cotton-wool, pin, etc., would pass more slowly, and the 'say when' would become a little more rapid and insistent, as the correct boundary was approached." His ward rounds and demonstrations were crowded, post-graduates and students alike being attracted by his gift of exposition, enthusiasm, and sense of the dramatic. He would illustrate his lectures by himself reproducing the involuntary movements or postures produced by nervous disease, and "Henry Head doing gaits" was a perennial attraction. As Sherrington (1940) characteristically put it: "As a teacher he had himself a wide and devoted following. In his lecturing some slight mannerisms endeared themselves to his audience as very symbols of him."

After the first world war, when the establishment of medical professorial units was being considered, it was suggested that Head might become the first professor of medicine at the London. Indeed the proposal got as far as the preparation by him of a memorandum on the constitution of such a unit, which in his view needed 100 beds and three whole-time assistants. But it was not to be. It would have been an exciting experiment, for Head had long held distinctive views of his own on medical education. Nearly twenty years previously he had written in his diary: "Medical education in England suffers from the fact that the great hospitals are manned by practitioners of medicine who sometimes teach, instead of by professors of that science who occasionally practise."

Until the first world war the London was the only hospital at which Head was on the staff. Then the Empire Hospital for Officers was set up in Vincent Square, where officers suffering from wounds involving the nervous system were concentrated. Head was a civilian consultant and there he was joined by George Riddoch, who had recently come down from Aberdeen to take a resident post at the West End Hospital for Nervous Diseases and became Officer-in-Charge. Once again Head took into partnership in research an able young man, and one of the results was the series of papers on the effects of gross injuries of the spinal cord. This work was perhaps of less theoretical novelty than his earlier researches on sensation, but it was of great practical importance, since it laid the foundations of the management of traumatic paraplegia, of which Riddoch was to be an apostle in the second world war, and which undoubtedly saved many lives, and did much to maintain the health of the survivors.

In 1904, when he was 42, Head married Ruth Mayhew, daughter of Anthony Mayhew, Chaplain of Wadham College, Oxford. She was headmistress of Brighton High School for Girls, and a fit companion for him in intelligence and breadth of interest. They had no children, but Ruth Head once said that this had been more than compensated for by

the part he had played in her life. They had known each other for seven years before they married, and, being separated by their work, they started a joint diary and commonplace book. Each had a volume, which they exchanged from time to time, so that they could comment on each other's experiences, thoughts and reading. Ruth Head herself wrote several books, including two novels, and compiled an anthology of Thomas Hardy's writings, to which Henry wrote an introduction. As Sir Gordon Holmes wrote in his Royal Society obituary, "she shared his interests, stimulated his enthusiasms, criticized his writings and relieved him of many of the petty worries of life. In his later years she was his constant companion, and her philosophical outlook, her joy in life and her encouragement helped him to bear an illness which otherwise would have been an intolerable fate to one of his active mind and body." Ruth Head died a year before her husband.

We cannot think of Henry Head only as a doctor. Like Whitman he might have said: "I am large, I contain multitudes." And, again like Whitman: "When I give, I give myself." His interests were wide, and embraced art, literature, the stage, music, and, indeed, all aspects of human nature. A poet himself, he published "The Destroyers" a book of very personal verse, and, had he not adopted medicine as a profession, he might well have been equally distinguished as a writer. He reminds one of what Boswell and Johnson said about Burke. "Boswell: Mr. Burke has a constant stream of conversation. Johnson: Yes, Sir; if a man were to go by chance at the same time with Burke under a shed to shun a shower, he would say—'this is an extraordinary man'." It was natural that one with so many gifts, and so ready to give, should attract a circle of gifted people. He was the friend and doctor of the poet W. E. Henley, and during and after the first world war counted among his friends some of the younger Georgian poets, among them Siegfried Sassoon, Robert Graves, and Robert Nichols. To them, as to many young people in many walks of life, he was a kind of universal uncle, Uncle Harry. Let me quote the impression he made upon one of them. Robert Nichols wrote about him in *The Times*: "Sir Henry possessed the fullest as well as the wisest mind I have ever known. It was no unusual thing to hear him in the course of one evening discourse on topics so various as: the influence of reasoning upon Goethe and Mozart, types of apprehension in listeners to symphonic music, sensations while looping the loop (he was over 60 when he did so), the painting of Guardi, 'co-ordination' in a star golfer, Ninon de Lenclos, Conrad as a narrator (Sir Henry was far the ablest literary critic I have ever known), religious ecstasy, the relation of art and science, the social customs of Melanesia. On each of such topics he not only appeared to have more information than anybody in the room, but spoke after a more illuminating fashion,

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for, like Leonardo (on whom he was an authority) he had a supreme eye for the significant. Nor did he resemble Leonardo in mind only. He had Leonardo's lofty human compassion, humility, patience, and profound serenity of spirit."

With the first symptoms of Parkinsonism Head retired from the London in 1919, and shortly afterwards, at the suggestion of Siegfried Sassoon, went to live in Dorset as the neighbour of Thomas Hardy at Max Gate. This new friendship was a consolation to both of them, but Hardy had not long to live, and soon after his death the Heads moved to Hartley Court, near Reading, to be nearer London. Harvey Cushing (Fulton, 1946) describes in detail a visit he paid to him there. The last time I saw Henry Head was a few months before he died. He was 78, and for many years had been quite immobilized by his Parkinsonism, and had great difficulty in speaking. But his mind was still alert, and he was eager to know what was happening in neurology. He talked about his own disabilities, and the physical obstacle they put in the way of speech, the part played by the auditor in speech, the body-image, and sensory projection. He pointed out that a walking-stick becomes temporarily part of one's body-image, so that when one touches the ground with its tip, the resulting sensations, though felt in the hand, are projected to the end of the stick. "Lotze," he said, "remarked that a woman could project to the end of the feather in her hat," and added that "a well-made dental plate is part of one's body, but it you get a pip under it, it becomes a foreign body."

So one hundred years after he was born we today recall this vivid personality. The other speakers this afternoon have discussed some of his ideas. Apart from his work on sensation and speech, his concepts of the schema and vigilance were far ahead of his time, the latter an anticipation of much recent work on the physiology of attention. He had many ideas: he bubbled over with them, and perhaps he was sometimes too ready to convince himself of their truth. But no original thinker has lacked critics ready to point that out. The progress of science depends upon the ability to ride with a foot on each of two horses, one named Fact and the other Hypothesis, and the problem always is to keep them running level. Head contributed to neurology new facts and new ideas. More important perhaps than either was his vitalizing influence upon those with whom he worked, those he taught, and those he is still teaching, and will continue to teach.

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# SOME FURTHER OBSERVATIONS UPON THE EFFECT OF UNILATERAL CEREBRAL LESIONS ON CALORIC AND ROTATIONAL NYSTAGMUS

BY

E. A. CARMICHAEL,[1] M. R. DIX,[2] C. S. HALLPIKE,[2] AND J. D. HOOD[2]

## INTRODUCTION

WITH certain unilateral cerebral lesions there is known to occur a characteristic derangement of vestibular nystagmus. This was first described by Bauer and Leidler (1911) and later confirmed by Dusser de Barenne and de Kleyn (1923).

They showed very clearly that following the removal of one cerebral hemisphere in the rabbit, e.g. the left, any rotational or caloric stimuli which produced nystagmus with its rapid component to the left—in conventional parlance, vestibular nystagmus to the left—were more effective than their opposites. There was, in fact, a preponderance of induced vestibular nystagmus towards the side of the lesion.

In the course of previous work (Carmichael, Dix and Hallpike, 1954) systematic examinations of vestibular function were carried out in a considerable number of human subjects with unilateral cerebral lesions, with a view to ascertaining whether this directional preponderance effect could be attributed to organic damage of a particular part of the hemisphere.

The methods of examination and results will first be briefly reviewed.

Vestibular nystagmus was induced by means of the standardized method of caloric stimulation described by Fitzgerald and Hallpike (1942); the

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stimuli being applied with the subject supine on a couch and the head raised some 30 degrees above the horizontal, thus bringing the external semicircular canal into the vertical plane, its position of maximum sensitivity to thermal stimuli. For the cold and hot stimuli, water is used at temperatures of 30° and 44° C.—7° below and above body temperature, and with these the external auditory meatuses are irrigated in succession for periods of 40 seconds. The effects are substantially limited to the external semicircular canals and are calculated to bring about equal and opposite deflections of the cupulae. The evoked nystagmic reactions are observed under good conditions of illumination and their duration measured. Throughout the tests active optic fixation is maintained by the subject upon a point in the straight ahead line of gaze.

In fig. 1 is shown the results in an average normal subject. The two continuous lines represent time—3 minutes subdivided into 20 second intervals. The interrupted lines represent the nystagmic responses.

Above are the two responses, left and right, to the cold stimuli. Their durations are about two minutes. The responses to the hot stimuli are rather shorter, 1 minute 40 seconds. The responses are numbered for reference 1 to 4 from above downwards; responses 1 and 4 consist of nystagmus to the right; responses 2 and 3 of nystagmus to the left.

In fig. 2 are shown nystagmus patterns characteristic of directional preponderance. Above, with directional preponderance to the right, responses 1 and 4 are increased, responses 2 and 3 are diminished. Below, with directional proponderance to the left, this is reversed.

The caloric tests were carried out in this way in a series of subjects with unilateral cerebral lesions. It was found that the responses exhibited no directional preponderances, nor indeed any abnormality unless the lesions had a particular localization within the hemisphere.

Thus, in fig. 3, Plate LV, are shown a number of lesions scattered about the frontal, parietal and anterior temporal zones. In these subjects the caloric responses were normal. In fig. 4 are shown a number of lesions localized within the posterior part of the temporal lobe. In all of these subjects there was a marked directional preponderance of caloric nystagmus to the side of the lesion.

It follows that in subjects with unilateral cerebral lesions the occurrence of directional preponderance of caloric nystagmus, at any rate as revealed by means of the test procedure specified, with active optic fixation, constitutes a physical sign of some practical importance indicating the involvement of the posterior part of the temporal lobe, towards which the nystagmic preponderance is directed.

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In 1958, Hakas and Kornhüber, from Jung's Clinic in Freiburg, published the results of an extensive study of the nystagmic responses to rotation in a large series of subjects with unilateral cerebral lesions. They used impulsive rotational stimuli with electro-nystagmographic recording of nystagmus. One other point of importance—all tests were carried out with the eyes closed, thus eliminating optic fixation.

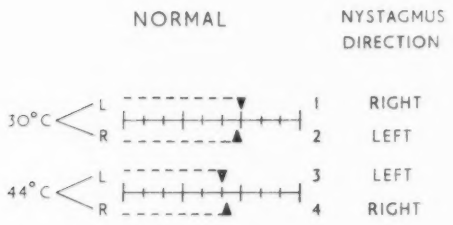


FIG. 1.

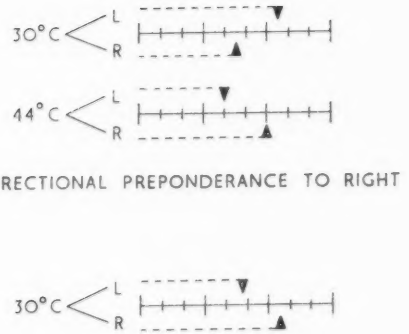


FIG. 2.

Their conclusions, very different from those of Carmichael, Dix and Hallpike, were that when directional preponderance did occur, it bore no relationship to a lesion in a particular part of a particular hemisphere. Furthermore, with unilateral temporal lobe lesions, a directional preponderance of rotational nystagmus, if it occurred at all, would be rather more likely to be directed towards the unaffected than to the affected hemisphere. They further concluded that vestibular tests were of no value in the localization of cerebral lesions.

Hakas and Kornhüber's paper is open to certain criticisms. Thus, it contains no comment upon the fact that their test procedure differs from that specified by Carmichael, Dix and Hallpike in one very important respect, namely, that all their tests were carried out with the eyes closed, thus abolishing optic fixation. In fact, they leave it to be inferred that they repeated the observations of Carmichael, Dix and Hallpike with quite different results.

*Present Investigations*

In the investigation now to be reported, an endeavour has been made to ascertain whether or not the striking disparity between the results reported on the one hand by Carmichael, Dix and Hallpike and on the other by Hakas and Kornhüber can be attributed to differences of the techniques and physiological conditions of the test procedures employed.

The material for the investigation consisted of a group of 10 subjects.

All had known unilateral cerebral lesions with involvement of the posterior part of the temporal lobe, and in five of these unilateral hemispherectomy had been carried out. Clinical data relating to these 10 subjects are given in Table I.

TABLE I.—CLINICAL SUMMARY

| *Case No.* | *Name* | *Age* | |
|---|---|---|---|
| 1 | L. A. | 12 | Fits, temper, tantrums, L. hemianopia since chicken pox, aged 2½ years. Mentally backward, L. homonymous hemianopia, sensory disturbance L. side of body and limbs. 9.4.52 Operation revealed widespread abnormality R. hemisphere. Angiomatous area 6 cm. diameter excised. Examination of ears, nose and throat: normal. Hearing: normal. (Pure tone audiogram.) |
| 2 | I. P. | 34 | Temper tantrums and R. hemiplegia following pertussis aged 18 months. R. homonymous hemianopia. R. lower facial palsy, sensory disturbance R. side of body. L. hemispherectomy 11/2/53. Examination of ears, nose and throat: normal. Hearing: normal. (Pure tone audiogram.) |

TABLE I.—CLINICAL SUMMARY—*contd.*

| *Case No.* | *Name* | *Age* | |
|---|---|---|---|
| 3 | V. S. | 18 | Epilepsy since aged 11 years. Slight weakness and incoordination L. limbs. EEG showed R. mid-posterior temporal focus. Local cortical excision 18/3/60. Examination of ears, nose and throat: normal. Hearing: normal. (Pure tone audiogram.) |
| 4 | B. T. | 24 | Fits since bomb incident aged 5 years. L. homonymous lower quadrantic hemianopia. Diplopia L. lateral gaze. Partial removal of cyst of R. parieto-temporal area by diathermy 6/10/49. Examination of ears, nose and throat: normal. Hearing: normal. (Pure tone audiogram.) |
| 5 | M. S. | 48 | Pain R. eye, numbness L. arm and leg, L. hemiplegia ten days. Improving. Impaired sensation L. side of body. Arteriogram showed cerebral lesions R. parieto-temporal area. R. carotid occlusion. Examination of ears, nose and throat: normal. Hearing: normal. (Pure tone audiogram.) |
| 6 | J. S. | 26 | Epilepsy since 1945. L. temporal lobectomy 1954. Fits recurred 1959. L. meningo-cortical cicatrix behind Labbe's vein. L. mid-temporal cortex excised 21/1/60. R. upper quadrantic homonymous hemianopia post-operatively. Examination of ears, nose and throat: normal. Hearing: normal. (Pure tone audiogram.) |
| 7 | B. C. | 28 | L. hemiplegia since birth. Minor epilepsy since aged 5. Mental retardation and behaviour disorder. L. homonymous hemianopia. Impaired sensation L. hand. R. hemispherectomy 19/9/60. Examination of ears, nose and throat: normal. Hearing: normal. (Pure tone audiogram.) |
| 8 | C. S. | 22 | Febrile illness aged 1 year followed by L. hemiplegia and epilepsy. L. hemianopia. Diminished sensation L. arm and face. R. hemispherectomy 23/7/55. Examination of ears, nose and throat: normal. Hearing: normal. (Pure tone audiogram.) |
| 9 | P. L. | 25 | Convulsions aged 10 months followed by L. hemiplegia. Epilepsy since aged 10 years. L. homonymous hemianopia. Depressed sensation in L. face, body and limbs. R. hemispherectomy 9/7/58. Examination of ears, nose and throat: normal. Hearing: normal. (Pure tone audiogram.) |
| 10 | T. S. | 19 | Measles aged 13 months with convulsions followed by L. hemiplegia. Epilepsy since aged 8 years. L. homonymous hemianopia. R. hemispherectomy 23/6/55. Examination of ears, nose and throat: normal. Hearing: normal. (Pure tone audiogram.) |

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## Methods and Results

The investigation consisted of a systemic study of caloric and rotational nystagmus. The nystagmic responses were observed directly and also recorded electro-nystagmographically. For details of the electro-nystagmographic technique, references should be made to a previous publication (Hallpike, Hood and Trinder, 1960).

All of the tests were first carried out with active optic fixation and thereafter repeated in total darkness with the eyes open. Under these conditions optic fixation was abolished.

### (1) *Induced Vestibular Nystagmus with Optic Fixation*

(*a*) *Caloric stimulation.*—This was carried out according to the standard procedure of Fitzgerald and Hallpike (1942), with active optic fixation. The nystagmus durations were assessed as usual, by direct observations of the subject's eyes and in all 10 subjects there was a marked directional preponderance to the side of the lesion. The tests were then repeated with electro-nystagmographic recording of the nystagmus. The results were substantially the same; that is to say, the nystagmus durations derived from the records showed the same directional preponderance as clearly but no more clearly than direct observation of the eyes.

(*b*) *Rotational stimulation.*—For this, impulsive accelerations and decelerations were applied, up to and from rotational velocities of 60°/sec. to the right and to left. Thus four stimuli in all were applied. With rotation to right the "start" and "stop" stimuli evoked nystagmus to right and to left respectively. With rotation to left the "start" and "stop" stimuli evoked nystagmus to the left and right respectively.

Active optic fixation was maintained upon a light source rotating with the subject in the straight ahead line of gaze. Apart from this fixation point, the tests were carried out in darkness, and the nystagmus evaluated from the electro-nystagmographic records. As with the caloric tests carried out with active optic fixation, the records showed the same directional preponderance to the side of the lesion.

### (2) *Induced Vestibular Nystagmus without Optic Fixation*

In this series both the caloric and the rotational tests were repeated with one important modification. They were carried out with the subject's eyes open but in complete darkness. As with Hakas and Kornhüber's tests, optic fixation was now abolished. In fact, the conditions differed from those of their tests in one respect only—darkness instead of eye closure being used for the abolition of fixation. The nystagmographic findings now showed some striking alterations. Firstly, the amplitude of

NYSTAGMIC RESPONSES TO IMPULSIVE ROTATIONAL STIMULI (60°/SEC.)
EYES OPEN. OPTIC FIXATION.

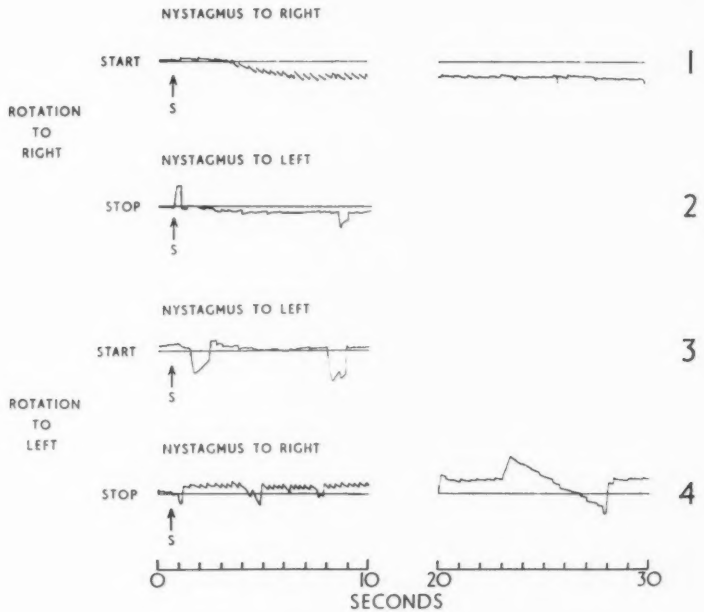


FIG. 5.

the nystagmus was greatly increased. This was not surprising. Since vestibular nystagmus is known to be inhibited with optic fixation its enhancement without it was to be expected. A second and more important difference was the effect upon directional preponderance. Thus, in all 10 subjects, with both the rotational and the caloric tests, the directional preponderance to the side of the lesion, so evident with optic fixation, was absent or reversed without it.

Typical nystagmographic responses to rotational stimuli from a subject (No. 8 Table I) with a right sided cerebral lesion are shown in figs. 5 and 6.

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The records shown in fig. 5 were obtained with optic fixation and it will be seen that responses 1 and 4, consisting of nystagmus to the right, are much greater than responses 2 and 3 consisting of nystagmus to the left. In other words there is a well marked directional preponderance to the right, the side of the lesion.

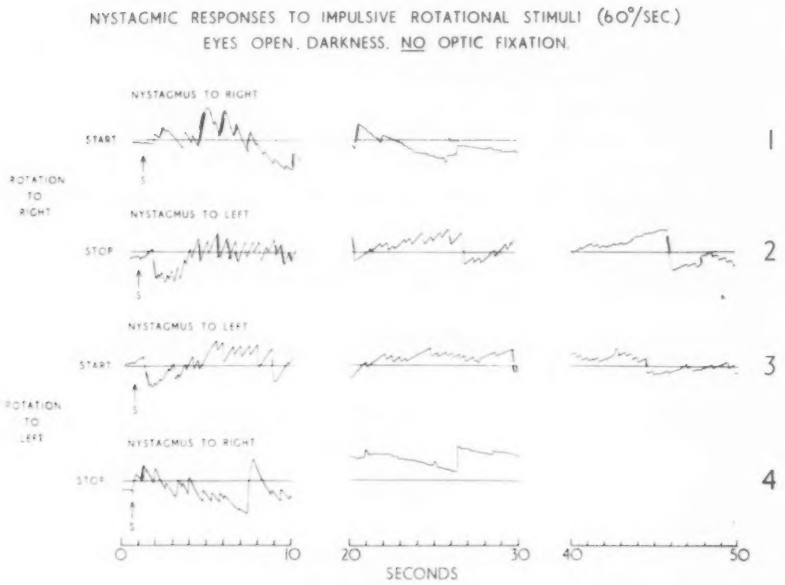


FIG. 6.

The records shown in fig. 6 were obtained with the eyes open in darkness, i.e. without optic fixation.

In contrast to the responses shown in fig. 5 responses 2 and 3, consisting of nystagmus to the left, are greater than responses 1 and 4, consisting of nystagmus to the right. In other words, the directional preponderance to the right with optic fixation has been reversed without it.

Complete data for all 10 subjects relating to spontaneous and induced vestibular nystagmus and to optokinetic nystagmus are given in Table II.

TABLE II.—SPONTANEOUS NYSTAGMUS, EYE DEVIATION WITH ABOLITION OF FIXATION, DIRECTIONAL PREPONDERANCE OF OPTOKINETIC NYSTAGMUS AND OF CALORIC AND ROTATIONAL NYSTAGMUS WITH AND WITHOUT OPTIC FIXATION

| *Case No.* | *Name* | *Age* | *Side of lesion* | *Spontaneous nystagmus* | *Deviation of eyes with abolition of fixation* | | *Optokinetic nystagmus* | *Caloric nystagmus* | | *Rotational nystagmus* | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | *Eye closure* | *Darkness* | | *Fixation* | *No fixation* | *Fixation* | *No fixation* |
| 1 | L. A. | 12 | R | 1st° —→ | ←— | Nil | —→≫ | — | — | —→≫ | ←— |
| 2 | I. P. | 34 | L | 2nd° ←— | —→ | —→ | ≪— | ←— | ←→ | ≪— | ←→ |
| 3 | V. S. | 18 | R | 1st° —→ | —→ | Nil | —→≫ | —→ | ←→ | ←→ | ←— |
| 4 | B. T. | 24 | R | 1st° —→ | ←— | Nil | —→≫ | —→≫ | ←— | —→ | ≪— |
| 5 | M. S. | 48 | R | Nil | ←— | ←— | —→≫ | —→≫ | ≪— | — | ←→ |
| 6 | J. S. | 26 | L | Nil | —→ | —→ | ←— | ←— | ←→ | ←→ | ←→ |
| 7 | B. C. | 28 | R | 2nd° —→ | —→ | —→ | —→≫ | —→≫ | ←→ | —→≫ | ←— |
| 8 | C. S. | 22 | R | 3rd° —→ | ←— | ←— | —→≫ | —→≫ | ≪— | —→≫ | ≪— |
| 9 | P. L. | 25 | R | 2nd° —→ | ←— | ←— | —→≫ | —→≫ | — | —→≫ | ←— |
| 10 | T. S. | 19 | R | 1st° —→ | ←— | Nil | —→≫ | —→≫ | ≪— | —→≫ | ←— |

Preponderance to left ←—
Marked preponderance to left ≪—
No preponderance <—>
Preponderance to right —→
Marked preponderance to right —→≫

## Discussion

To summarize these findings, it seems quite clear that directional preponderance as a physical sign of certain unilateral cerebral lesions will certainly manifest itself if the vestibular stimulation is applied with optic fixation maintained.

This conclusion seems to be supported by the recent work of Sandberg and Zilstorff-Pedersen (1961) who carried out caloric tests in a series of subjects with unilateral temporal lobe lesions. They employed the technique used by Carmichael, Dix and Hallpike (1954), with optic fixation maintained and confirmed the occurrence of directional preponderance to the side of the lesion.

By contrast, the findings now reported show that if the vestibular stimuli are applied under the conditions used by Hakas and Kornhüber (1959), that is to say without optic fixation, then this directional preponderance will be abolished or reversed.

In fact, the present investigation, while substantiating the findings of Carmichael, Dix and Hallpike on the one hand and of Hakas and Kornhüber on the other, seems to indicate optic fixation as the factor which determines the difference between them. If this be correct, then it remains to explain the way in which the factor operates.

The problem presents several aspects. To begin with, the fact that directional preponderance towards the affected hemisphere should be so clearly dependent upon optic fixation makes it difficult to accept the explanation previously offered by Fitzgerald and Hallpike (1942) that it is due to the elimination of certain hypothetical vestibular elements in the posterior part of the temporal lobe, or in fact to regard it as being in any sense a disturbance of vestibular function. However, the situation is far from being a straightforward one, and it is necessary to consider certain complicating factors. Of these, the most obvious is the effect of conjugate ocular deviations known to occur in the absence of optic fixation in association with certain unilateral cerebral lesions, in particular those causing hemiparesis. Thus, Bárány (1913) writing on this subject, gives a particularly valuable description of marked deviation of the eyes occurring with eye closure towards the paralysed side. Such a deviation would clearly have a considerable effect upon any induced vestibular nystagmus, which is known to be enhanced by deviation in the direction of the rapid component of the nystagmus, and inhibited by the opposite. Thus, in the case of a right-sided cerebral lesion the eyes, on eye closure, would characteristically deviate towards the left. As a result, a real vestibular abnormality —a directional preponderance of induced vestibular nystagmus to the right—could well be abolished or reversed solely by virtue of a concomitant deviation of the eyes to the left.

It will be seen from Table II that in 8 of the 10 subjects the abolition of fixation was accomplished, as Bárány described, by a deviation of the eyes

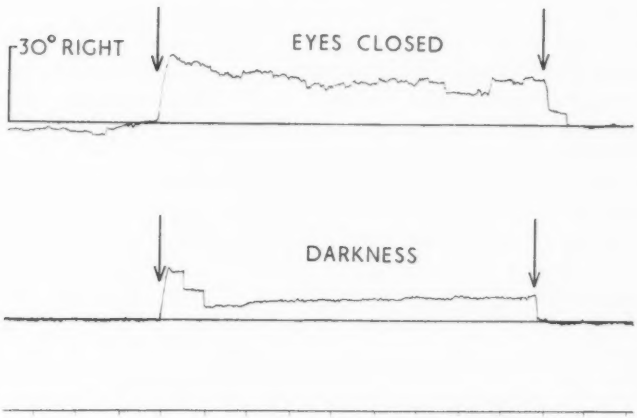


FIG. 7.—Eye deviations from the straight ahead position of gaze resulting from eye closure or darkness in a subject with a left cerebral lesion (Table I, Case 6).

to the side opposite to the cerebral lesion. It has been of interest to note, too, that as shown in fig. 7 this deviation was more marked with eye closure than in darkness.

This finding certainly favours the possibility that in most, at any rate, of the cases included in the present series, eye deviations, occurring in the absence of fixation, may have been a factor tending to mask a directional preponderance of caloric or rotational nystagmus to the side of the cerebral lesion.

The apparent dependence upon optic fixation of the finding in cases of unilateral temporal lobe lesions of ipsilateral directional preponderance of induced vestibular nystagmus, might, it seems, also be attributed, at any rate in part, to disturbances of optokinetic nystagmus with which these lesions may be associated. Thus, reference to Table II shows that in all of the 10 cases there was a directional preponderance of optokinetic nystagmus to the side of the lesion, or, as it is usually expressed, a partial suppression of optokinetic nystagmus to the opposite side.

The following is suggested as a possible mechanism whereby, in the case of a right temporal lobe lesion, a directional preponderance to the right of induced vestibular nystagmus might be masked or reversed by a concomitant suppression of optokinetic nystagmus to the left.

If, in such a subject, under the usual caloric test conditions, a hot stimulus be applied to the right ear, vestibular nystagmus develops with its rapid component to the right. The eyes will execute slow excursions to the left, in the course of which the images of stationary objects will be displaced towards the left sides of the retinæ. They therefore appear to move to the subject's right.

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Now, much the same visual conditions are reproduced if an optokinetic drum is rotated to the right of a subject with stationary eyes. When this is done, the eyes will execute reflex optokinetic nystagmus with slow movements, following the drum, to the right, followed by rapid movements to the left—in conventional terminology—optokinetic nystagmus to the left. Thus, it can be argued that vestibular nystagmus to the right, with optic fixation maintained, normally evokes and is checked by a secondary optokinetic nystagmus to the left.

If this argument be applied to the case of a right cerebral lesion without any real directional preponderance of induced vestibular nystagmus, but with suppression of optokinetic nystagmus to the left, then caloric or rotational nystagmus to the right will be unchecked by the normal secondary optokinetic nystagmus to the left. Hence, if the tests are carried out with optic fixation maintained there will be a directional preponderance of induced vestibular nystagmus to the right—the side of the lesion.

Although this argument might explain the occurrence of directional preponderance of induced vestibular nystagmus to the side of the cerebral lesion, in those of our subjects in whom there was an associated defect of optokinetic nystagmus to the opposite side, it will not explain it in others. It may be recalled, for example, that in a substantial group of the subjects studied by Carmichael, Dix and Hallpike (1954) with posterior temporal lobe lesions and ipsilateral directional preponderance of caloric nystagmus, there was no abnormality of optokinetic nystagmus. Although it must be said of the results of the present investigation that they cast doubt upon the existence, as a true vestibular effect, of an ipsilateral directional preponderance of induced vestibular nystagmus in association with unilateral posterior temporal lobe lesions, nevertheless they do not wholly exclude it. The truth is perhaps that the effect does exist, although, as Fitzgerald and Hallpike (1942) pointed out, it is, in its uncomplicated form, quite a small one. For this reason it tends to be overshadowed by other factors, being exaggerated by concomitant disturbances of optokinetic nystagmus or obscured by ocular deviations which occur in the absence of optic fixation.

A study of the recordings obtained in the course of the present investigation emphasizes the value of electro-nystagmographic recording systems of the modern direct current type capable of providing accurate records of sustained ocular deviations. It emphasizes, too, the instability of the eyes when deprived of the controlling influence of optic fixation. In this state, comparable to that of a well balanced undamped compass needle, very slight imbalances of the several nystagmogenic forces arising from various sources within the vestibular system—the hemispheres, the cerebellum, the vestibular nuclei and elsewhere—are likely to be reflected in considerable directional preponderances of induced nystagmus.

This and the multiplicity of the nystagmogenic mechanisms must clearly make the task of their analysis one of great complexity.

SUMMARY

(1) A description is given of the nystagmic responses to caloric and rotational stimulation in 10 subjects with unilateral cerebral lesions involving the posterior part of the temporal lobe.

(2) The nystagmus was evaluated by direct observation of the eyes and from electro-nystagmographic records. For the recording system direct current amplification was used of the corneo-retinal potentials, and with this it was possible to make accurate observations of any sustained conjugate eye deviations occurring when optic fixation was abolished by eye closure or darkness.

(3) Two series of observations were made. For the first, optic fixation in the straight ahead line of gaze was maintained according to the test procedure used in previous investigations by Fitzgerald and Hallpike and by Carmichael, Dix and Hallpike.

In confirmation of their results a marked directional preponderance towards the side of the lesion was found to occur in all 10 subjects.

The second series of observations was carried out in the manner of Hakas and Kornhüber with optic fixation abolished.

Under these conditions the directional preponderance of induced nystagmus towards the side of the lesion observed to occur with optic fixation was found to be abolished or reversed.

(4) The results, in addition to confirming the findings of Fitzgerald and Hallpike and of Carmichael, Dix and Hallpike, are found to be in agreement also with the findings of Hakas and Kornhüber who have reported, *inter alia*, that any directional preponderance of induced nystagmus occurring in unilateral temporal lobe lesions is more likely to be directed towards the unaffected than towards the affected hemisphere.

(5) Emphasis is laid upon the finding that the occurrence of directional preponderance of induced nystagmus to the side of the lesion appears to be dependent upon the maintenance of optic fixation in the straight ahead line of gaze as part of the test procedure, and the possibility is suggested that the abolition or reversal of this directional preponderance when the tests are carried out in the manner of Hakas and Kornhüber with the eyes closed, might be due to conjugate deviations of the eyes which may occur under these conditions.

In support of this possibility it is noted that in 8 of the 10 subjects examined in the course of the present investigation, clear electro-nystagmographic evidence was obtained of the occurrence of such deviations, occurring as described by Bárány towards the side opposite to the lesion, and likely for this reason to cancel or reverse any directional preponderance of nystagmus to the side of the lesion present with optic fixation maintained in the straight ahead line of gaze.

(6) The further possibility is suggested that directional preponderance of induced vestibular nystagmus to the side of a unilateral temporal lobe

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lesion might in some cases be due to a concomitant defect of optokinetic nystagmus towards the opposite side.

It is emphasized that this possibility only exists in such cases in which this optokinetic defect was present. It would not exist in others in which, as described by Carmichael, Dix and Hallpike, optokinetic nystagmus is normal.

(7) It is concluded that the phenomenon of ipsilateral directional preponderance of induced vestibular nystagmus in unilateral lesions involving the posterior part of the temporal lobe is a real phenomenon. Nevertheless, in its uncomplicated form, it is, as emphasized by Fitzgerald and Hallpike, a small one and therefore likely to be obscured or exaggerated in a manner dependent upon the conditions of the test procedure, in particular, the maintenance or otherwise of optic fixation and by concomitant defects of optokinetic nystagmus.

(8) The investigation stresses the value of electro-nystagmographic recording systems capable of providing accurate records of sustained ocular deviations.

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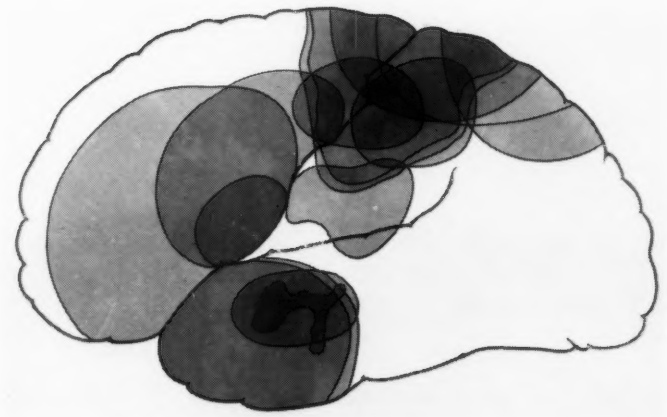

FIG. 3.

FIG. 4.

*To illustrate article by E. A. Carmichael, M. R. Dix, C. S. Hallpike and J. D. Hood.*

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# ON THE RELATIONSHIP OF METACHROMATIC LEUCODYSTROPHY AND AMAUROTIC IDIOCY

BY

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THE existence of a close and pathogenetically significant relationship between amaurotic family idiocy and metachromatic leucodystrophy has frequently been suggested on both morbid anatomical and biochemical grounds. Two morphological observations support this hypothesis: *first*, the occurrence of lipid storage within the cytoplasm of neurones of certain fairly constant nuclear groups in cases of metachromatic leucodystrophy (Wicke, 1938; Norman, 1947; Brain and Greenfield, 1950; Greenfield, 1950; Leslie, 1952; Peiffer and Hirsch, 1955; Jervis, 1958, 1960; and others) and *secondly* the presence in some cases of amaurotic family idiocy of large areas deficient in myelin but containing, in addition to neutral fats, substances called prelipids (Ostertag, 1925; Bérard-Badier, *et al.*, 1958). From a biochemical viewpoint, an increase in the hexosamine and neuraminic acid content of the brain has been found in both conditions; in metachromatic leucodystrophy this increase is in the white matter (Edgar, 1955*a* and *b*) while in amaurotic idiocy it has been observed in samples of grey matter (Cumings, 1953).

The object of this paper is to describe the pathological findings in 3 siblings who exemplify this association in remarkable degree and to discuss the results of histochemical and biochemical studies.

The 3 sibs who form the subject of the present report come from a sibship of 5 in a French-Canadian family (fig. 1). The parents are young, healthy and not consanguineous. There was no neurological disease in the parents' or grandparents' generations. The two youngest siblings in this family, twins born in 1957, are developing normally, and examination at the age of 3 years did not reveal any abnormality suggestive of the disease which involved the older siblings.

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## Clinical Histories

*Case* 1.—The oldest child, a boy André, was delivered normally following a full term, normal pregnancy. His development was slightly retarded from birth. He sat up at 8 months, stood with support at the age of 1 year but never walked independently. At the age of 2 years, he began to have episodes in which his eyes turned upwards, and during which he was unresponsive. At the same age he began to utter high-pitched cries. At about this time he had chickenpox and thereafter rapid mental and physical deterioration ensued; he stopped speaking and lost the ability to stand or sit upright. At the age of 2½ years he was admitted to the Montreal Neurological Institute. He was small, poorly developed, and poorly nourished. He lay quietly in bed without reaction

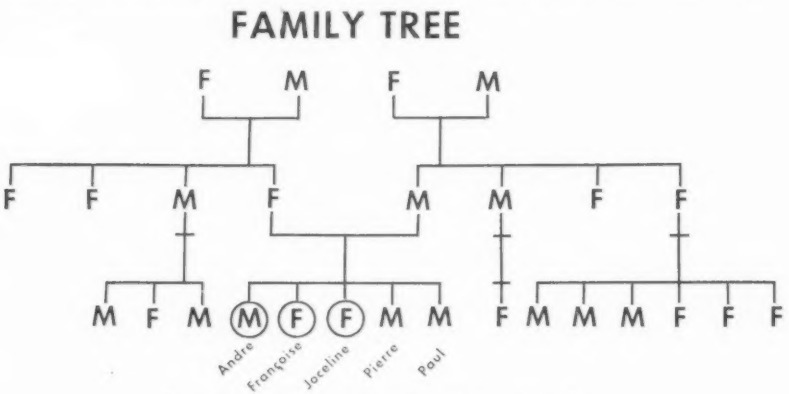


Fig. 1.—Family tree showing relationship of cases.

to his surroundings except for a high pitched cry when moved. The head was small, measuring 46 cm. in circumference. He did not follow objects with his eyes; he appeared to be blind. The pupils did not react to light but did react on occasions of spontaneous convergence. There was bilateral convergent strabismus. The optic fundi were normal; in particular there was no optic atrophy or abnormal retinal pigmentation. The child appeared to be deaf. The arms and legs were very spastic but some spontaneous movements were present. Tendon reflexes in the arms were very weak; the knee-jerks were brisk and the ankle-jerks doubtfully present. The plantar responses were extensor. Examination of chest and abdomen was non-contributory. Hæmogram, urinalysis and serological tests for syphilis gave normal results. Cerebrospinal fluid protein was 29 mg. per cent; no cells were present. An EEG showed severe diffuse abnormality. X-rays of the skull showed widening of the coronal suture. A ventriculogram showed great dilatation of lateral and third ventricles; the cerebral aqueduct was not visualized and was therefore considered to be obstructed. Because of this a ventriculo-cisternostomy was carried out and a biopsy specimen of brain obtained. His subsequent course was one of progressive deterioration and he died at home early in 1955 at just under 3 years of age. Unfortunately post-mortem examination was not obtained.

*Case* 2.—Françoise, the second child in the family, was two years younger than her brother André. Her delivery and early development were entirely normal. At the age of 14 months her parents noticed an arrest of her development and later a deterioration of her mental and physical status. At the beginning of her illness, she developed

difficulty in walking with a tendency to fall backwards. Later her sight gradually deteriorated. Gradual impairment of hearing ensued. She stopped walking and speaking, and eventually did not react to visual or acoustic stimuli. At no time was any abnormality observed in the ocular fundi. The illness was very slowly progressive. She died at the age of 5 years in a marasmic state. Full post-mortem examination was carried out.

*Case* 3.—Joceline was the third child in the family. She was $2\frac{1}{2}$ years younger than her sister, Françoise. Like her sister, she developed normally until the fifteenth month of her life; from then onwards she developed an almost identical illness. There was impairment of walking and arrest and later deterioration of her mental ability. She developed profound dementia, spasticity of all limbs and extreme marasmus. There was no significant abnormality of the ocular fundi. The course of her illness was more rapid than in Françoise's case, and she died at the age of three years, twenty months after the onset of her illness. Full post-mortem examination was carried out.

## Pathological Observations

*Case* 1.—In this case, only diagnostic brain biopsy was carried out. The biopsy material comprised cortex and white matter from the right parietal lobe. There was loss of normal cyto-architectural pattern in the cortex, only the molecular and the external granular layers being clearly identifiable. There was also a slight generalised loss of neurones. The majority of cortical neurones showed globular distension of their cell bodies. Their nuclei were displaced to the periphery, mainly towards the apical dendrites. Nissl granules were extremely scanty and the neuronal cytoplasm, when stained with ordinary chromatic dyes, had a pale, slightly reticulated or finely granular appearance. These granules were strongly positive when stained by the periodic acid Schiff reagent and with Sudan Black B. They were pale yellowish-orange in Sudan IV-stained, paraffin-processed sections. There was remarkable proliferation of glial cells, both astrocytes and microglia, within the cortex. In the white matter there was moderate pallor of myelin sheaths in Heidenhain's stain. This was accompanied by glial proliferation with hypertrophied astrocytes. The white matter and, to a much lesser degree, the cortex contained phagocytes filled with coarse granular material. This material was strongly positive in PAS preparations, pale grey in Sudan Black B, and entirely negative in Sudan IV. The cytoplasm of these phagocytes was not seen in cresyl violet-stained, paraffin sections. Preparations to demonstrate metachromasia were not made at the time of initial investigation and, as all the remaining material was embedded in paraffin, this property could not be assessed subsequently. Apart from these intracellular granular accumulations, there were some loose masses of granular material scattered throughout the tissue. Very slight perivascular lymphocytic infiltration was present.

*Case* 2.—At post-mortem examination, carried out about fifteen hours after death, the body was emaciated and there was generalized brown pigmentation of the skin. Bilateral tracheobronchitis and acute bronchopneumonia were present. There was no enlargement of the liver or spleen. Microscopic examination of the lungs confirmed the gross diagnosis. The changes seen in the other trunk organs, except the kidneys and liver, were insignificant. The liver showed fatty change of parenchymal cells and some neutral fat deposits within Kupffer-Browicz cells. Occasionally, single macrophages containing neutral fat were seen in the portal tracts. Several macrophages here also contained some granular material strongly positive with periodic acid Schiff reagent and with Sudan Black B. They were also metachromatic with aniline dyes. No metachromatic deposits were seen in the parenchymal cells of the liver. Changes indicative of Niemann-Pick's disease or Gaucher's disease were not found in either

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liver or spleen. Interesting changes were observed in the kidneys. The cytoplasm of cells forming some secondary convoluted tubules, collecting tubules and Henle's loops, contained coarsely granular, strongly eosinophilic material. This was bright rose-pink with PAS reagent and positive in Sudan Black B (fig. 2, Plate LVI). It gave also both pink and brown metachromasia with acetic acid cresyl violet and with tartaric acid thionin. The lumina of some convoluted and collecting tubules contained PAS positive metachromatic deposits which were partially hyaline, partially granular in appearance (fig. 3). The further histochemical analysis of these deposits will be described subsequently.

*Nervous system.*—On naked eye examination there was severe generalized atrophy of both the cerebral and cerebellar hemispheres. The brain weighed 633 grammes. The leptomeninges were thickened and opaque. The brain as a whole was slightly firmer in consistence than normal. The white matter had a greyish tinge, but there was no definite demyelination. The corpus callosum was very thin, and the ventricles dilated, more so on the left. The brain-stem and spinal cord were unremarkable.

*Histopathology of nervous system.*—Severe pathological changes were present in both grey and white matter. The cortex showed generalized neuronal loss and its normal laminar pattern was no longer apparent. In some areas status spongiosus involved all cortical layers, while in others it was restricted to one or two layers (fig. 4). These changes were most severe in insular and occipital cortex; no region was spared. All remaining cortical neurones had enlarged, distended cell bodies (fig. 5). Their voluminous cytoplasm contained fine granular accumulations which stained poorly by ordinary methods, were negative in Sudan IV, but strongly positive in Sudan Black B (fig. 6) and in PAS. This stored material completely filled the neuronal cytoplasm, pushing the nucleus towards the cell's periphery, in the majority of cases towards the apical dendrite. Nissl granules were completely lost. The neuronal changes were accompanied by marked glial reaction. Cortical oligodendroglia seemed to be decreased in number. There was intense astrocytic proliferation and hypertrophy. Numerous granular cells filled with yellowish deposits were scattered throughout the cortex. There were only occasional examples of hypertrophied microglial cells. There was considerable fibrogliosis in the cortex, most intense in the superficial cortical layers but, in several regions, involving the whole thickness of the cortex. Generally the intensity and distribution of cortical gliosis corresponded to the intensity of neuronal loss and tissue destruction. The subcortical grey structures were less affected than the cortex. However, they also showed accumulation of granular material within the cytoplasm of neurones, more especially large neurones. This variation in degree of the storage process was well seen in the striatum where small neurones were only slightly affected. The globus pallidus, thalamus, subthalamic nucleus, hypothalamic nuclei, red nucleus and substantia nigra showed an advanced degree of the storage process in their neurones. In all these structures, many macrophages filled with yellowish-brown granular material were present. These nuclei showed moderate fibrogliosis. The same storage process involved neurones throughout the brain-stem and spinal cord. It reached greatest intensity in the motor neurones of the cranial nerves and the anterior horn cells of the spinal cord. Neurones of the posterior root ganglia were also involved.

The centrum ovale was diffusely demyelinated. The degree of demyelination varied, being, in general, more intense in the deeper portions of the hemispheres, and there was some sparing of subcortical fibres (fig. 7). The corpus callosum was entirely devoid of myelin, as were the external and extreme capsules while the internal capsule was only partially demyelinated. In striking contrast to this, the ansa lenticularis, striopallidal fibres, internal and external laminæ of the globus pallidus, fornix, optic tracts and optic radiations were entirely normal in their myelin picture. The pyramidal tracts in the brain-stem and spinal cord were partially demyelinated; other long tracts in the brain-stem showed a much lesser degree of demyelination. The cerebellar white matter

also showed demyelination. An outstanding feature in the white matter was the presence of numerous, large macrophages scattered throughout the demyelinated areas (fig. 8). In many regions these cells occurred in between remaining nerve fibres; this arrangement was most prominent in dense, oriented white structures, such as the corpus callosum and internal capsule. The cytoplasm of these macrophages contained granules, both coarse and fine, which showed four fundamental staining properties: they were strongly positive in PAS, grey in Sudan Black B, entirely negative in Sudan IV, and metachromatic with aniline dues in acid solution. Their more detailed histochemical characterization will be discussed later. Two types of macrophages were distinguished by their size, distribution and some of their staining properties. One group comprised large round or oval granular cells occurring mainly in the deeper parts of the white matter where demyelination was complete or almost so; the cytoplasm of these cells stained very poorly with ordinary chromatic dyes, having a pale reticulated appearance with hæmatoxylin and eosin and failing to stain with Heidenhain's method for myelin. The other group comprised smaller cells occurring mainly in those areas where myelin breakdown was less advanced such as in the immediately subcortical white matter and around blood vessels; the granular deposits in the cytoplasm of these cells was eosinophilic and took on a deep blue colour with Heidenhain's myelin stain. We consider that the difference between these forms of macrophages resulted from different stages of myelin metabolism. Macrophages were found in all demyelinated areas of the central nervous system, including those areas where myelin breakdown seemed to be secondary, for example the pyramidal tracts. They also occurred in small numbers in sites where myelin was not obviously damaged as, for instance, among the striopallidal fibres. In the cortex, cells of this type were confined to the deeper layers. Small collections of granular, lipid containing material were found lying loose in the tissue. A small amount of sudanophilic material was detected in the perivascular spaces, both loose and within macrophages.

Silver impregnation showed much damage to the axis cylinders in the cerebral white matter. Demyelinated and partially demyelinated regions showed severe diffuse fibrogliosis. We did not find abnormal deposits within the cytoplasm of hypertrophied astrocytes except in one small focus. Oligodendroglial cells were decreased in number in all demyelinated areas and to a lesser degree in some regions where myelin breakdown was partial or had not occurred at all, for instance in the well myelinated striopallidal fibres.

Changes in the cerebellar white matter were similar to those seen in the centrum ovale. The cerebellar grey matter presented distinctive lesions. The granule cell layer was atrophic while the apparently selectively spared stellate cells of Golgi showed cytoplasmic storage. Many Purkinje cells had disappeared, their sites being indicated by empty baskets. The remaining Purkinje cells had distended cell bodies and fusiform swellings of their antler-like dendrites (figs. 9 and 10). Torpedo-shaped deformities were present on Purkinje cell axons within the granular layer (fig. 11). Bergmann's glia was proliferated and there was severe fibrogliosis of the molecular layer. Neurones of the dentate and fastigial nuclei showed storage changes. The cytoplasmic lipids in these deep nuclei were metachromatic.

The optic nerves, despite their well myelinated condition, contained occasional phagocytes filled with metachromatic lipid material. In the retina there was remarkable cellular loss in the outer nuclear layer and many rods and cones had disappeared; the inner nuclear layer was preserved. The ganglion cells were reduced in number, and those remaining were filled with finely granular material which stained positively with PAS and Sudan Black B; it was also faintly metachromatic with aniline dyes (figs. 12 and 13). Granular deposits of melanin pigment were seen scattered throughout the outer nuclear layer of the retina, the picture being that of retinitis pigmentosa.

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*Case* 3.—At autopsy, carried out about six hours after death, there was severe emaciation and acute bronchopneumonia. Microscopical examination of the kidneys revealed changes identical with those described in Case 2. In the spleen there were occasional clusters of big cells with foamy cytoplasm; some of these gave a positive PAS reaction and stained black with Sudan Black B but were negative in Sudan IV; they were not metachromatic. The liver showed non-specific fatty change of the parenchymal cells. Occasional macrophages containing Sudan Black B and PAS positive material were seen in the portal tracts. The small gall-bladder was almost filled by a villous papilloma; numerous macrophages were present in its stroma and these contained lipid material with the same staining properties as that in the renal tubules (fig. 14). The other body organs were unremarkable.

*Nervous system.*—The brain was atrophic, weighing 695 grammes; this atrophy involved both cerebral and cerebellar hemispheres which were unusually firm. The leptomeninges were thickened and had a greyish tinge. The white matter was brownish-grey, but there was no evident demyelination on naked eye examination. The cortex in many areas seemed to be thinner than usual; in several places its inner border was not sharply defined. The ventricular system was symmetrically dilated. There were numerous heterotopic foci of grey matter in the ventricular walls bilaterally, mainly in posterior and inferior horns of the lateral ventricles (fig. 15). The brain stem and spinal cord were grossly unremarkable.

*Histopathology of nervous system.*—The microscopical findings in the nervous system were similar to those of Case 2 and we will therefore mention only the minor differences in intensity and distribution of the lesions. In Case 3, destruction of grey matter was more widespread and status spongiosus involved the whole thickness of the cortex more extensively (fig. 16). The caudate nucleus and putamen were involved while the globus pallidus and thalamus showed only a minor degree of neuronal loss. As in Case 2 the neuronal storage process was widespread and preferentially involved large neurones (fig. 17). Cerebellar involvement was more intense, especially in the palæocerebellum.

In contrast to the grey matter involvement, the white matter lesion was less marked than in Case 2. Areas in which demyelination was not complete were more numerous and this feature was most noticeable in the immediately subcortical white matter. Axis cylinder damage, however, appeared to be similar in degree. Macrophages containing eosinophilic material were more numerous and, in a greater proportion of them, this gave the staining reactions of normal myelin. Amongst these cells, more showed purple metachromasia with aniline dyes and fewer gave brown metachromasia. Changes in the optic nerves were similar to those in Case 2. The retinæ were not examined.

## Histochemical Observations

Histochemical studies were carried out in order to determine the nature of substances accumulated in various sites and to assess possible chemical relationships between them. In addition to the brain and spinal cord, studies were made of those body organs which, in ordinary chromatic stains, showed changes which were thought to be related to the fundamental pathological process. Table I gives a list of the methods used. Table II summarizes the histochemical findings in the nervous system. The histochemical properties of abnormal deposits in the retina, gall-bladder and kidneys are presented in Table III.

TABLE I

HISTOCHEMICAL METHODS USED

| STAINING METHOD | SUBSTANCES SHOWN |
|---|---|
| SUDAN IV | NEUTRAL FATS, CHOLESTEROL ESTERS |
| SUDAN BLACK B | LIPIDS |
| PERIODIC ACID-SCHIFF (PAS) | POLYSACCHARIDES, GLYCOPROTEINS etc. |
| PERFORMIC ACID-SCHIFF (PFAS) | LIPIDS CONTAINING UNSATURATED BONDS |
| ACETIC ACID-CRESYL VIOLET (PEIFFER-HIRSCH) | METACHROMASIA (CEREBROSIDE SULPHURIC ACID-ESTERS) |
| TOLUIDINE BLUE-STANDARD | METACHROMASIA |
| FEYRTER'S "MOUNTING" METHOD | METACHROMASIA-ACIDIC LIPIDS |
| ORCIN-HYDROCHLORIC ACID-METHOD | NEURAMINIC ACID (GANGLIOSIDES) |
| COPPER-PHTHALOCYANIN METHOD (KLÜVER) | CHOLINE CONTAINING PHOSPHATIDES & GLYCOLIPIDS |
| ALCIAN-BLUE METHOD (LISON) | ACID MUCOPOLYSACCHARIDES |
| OKAMOTO-SHIMAMOTO-UEDA METHOD | PHOSPHOLIPIDS AND CEREBROSIDES |
| OKAMOTO-SHIMAMOTO METH. AFTER PYRIDINE | PHOSPHOLIPIDS |
| OKAMOTO-SHIMAMOTO METH. AFTER ETHER | SPHINGOMYELIN |
| COUPLED TETRAZONIUM REACTION-DANIELLI | AROMATIC AMINO ACIDS (PROTEINS) |
| COUPLED TETRAZONIUM REACTION-BENZOYLATION | POLYMERISATION OF PROTEINS |
| MILLON'S REACTION | TYROSINE (PROTEINS) |

The solubility of the abnormal metabolic products in water, cold and warm (60°) acetone, ether, ethanol, methanol, petroleum ether, pyridine and a 2 : 1 mixture of chloroform and methanol was studied and the results are summarized in Table IV. In general, none of the solvents used abolished the capacity of the deposits to stain with Sudan Black B and with PAS. However, incubation in the chloroform-methanol mixture, hot acetone, absolute alcohol, petroleum-ether and in pyridine decreased the staining intensity of granular material both in macrophages and in neurones. These solvents completely abolished staining of extracellular granular material. We explain this phenomenon by the binding of stored intracellular deposits with cell protein, whereas the extracellular granules are not so bound. The positive coupled tetrazonium reaction of the intracellular deposits contrasted with the negative reaction extracellularly supports this explanation.

The metachromasia of lipids accumulated in macrophages was an outstanding feature in our cases. Despite generalized storage change in neurones, metachromasia of neuronal deposits occurred only in some nuclear groups; they were the dentate nucleus, globus pallidus, large pyramidal cells of the cortex and motor neurones of the spinal cord (fig. 18). With acetic acid cresyl violet (Peiffer and Hirsch, 1955), the metachromasia was purple and brown. The brown metachromasia occurred mainly in those areas where demyelination was more advanced, whereas purple metachromasia was seen in less demyelinated areas. When stained

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TABLE II

HISTOCHEMICAL PROPERTIES OF SUBSTANCES ACCUMULATED IN NERVOUS SYSTEM

| METHOD USED | GRAY MATTER | | WHITE MATTER | | |
|---|---|---|---|---|---|
| | NEURONES | METACHR. NEURONES | LARGE MACROPHAG. | SMALL MACROPHAG. | FREE DEPOSITS |
| SUDAN IV Frozen | – | – | – | – | – |
| SUDAN BLACK B Frozen | +++ | +++ | + | ++ | ++ |
| PAS Frozen | +++ | +++ | +++ | +++ | +++ |
| PAS Paraffin | ++ | ++ | ++ | ++ | ++ |
| PFAS Paraffin | – | – | – | – | – |
| ACETIC-ACID CRESYL VIOLET Frozen | – | + | +++ | +++ | +++ |
| TOLUIDINE BLUE-STANDARD Frozen | – | + | +++ | +++ | +++ |
| FEYRTER'S MOUNTING METHOD Frozen | + | ++ | +++ | +++ | +++ |
| ORCIN-HYDROCHLORIC ACID Frozen | + | + | – | – | – |
| ORCIN-HYDROCHLORIC ACID Paraffin | + | + | – | – | – |
| COPPER-PHTHALOCYANIN Paraffin | ++ | ++ | + | + | + |
| ALCIAN BLUE Paraffin | + | + | – | + | + |
| OKAMOTO METH. Frozen | ++ | ++ | +++ | +++ | +++ |
| OKAMOTO METH. AFTER PYRIDINE Frozen | ++ | ++ | – | + | – |
| OKAMOTO METH. AFTER ETHER Frozen | + | + | – | + | – |
| COUPLED TETRAZONIUM Paraffin | ++ | ++ | ++ | ++ | – |
| COUPLED TETRAZONIUM, BENZOYL Paraffin | ++ | ++ | ++ | ++ | – |
| MILLON'S METH. Paraffin | + | + | + | + | – |

\+ Faintly positive  +++ Strongly positive  – Negative
++ Positive  0 Test not done

by Feyrter's method (thionin in 0·5 per cent tartaric acid), the granular cells gave brown metachromasia as in the Peiffer-Hirsch preparations; neurones in general, including Purkinje cells and their distended dendrites, showed pink-violet coloration. The remaining myelin took as a rule a purple colour in acidic cresyl violet and tartaric thionin, but in some areas it was definitely brown, resembling the lipid deposits in granular cells. Metachromasia of granular cells disappeared entirely after one-and-a-half-hour incubation in pyridine, chloroform-methanol, chloroform-ethanol, and almost entirely after absolute alcohol and hot acetone. Cold acetone and ether did not have any influence on this staining phenomenon.

Sections examined in polarized light showed birefringence of abnormal

TABLE III

HISTOCHEMICAL PROPERTIES OF SUBSTANCES ACCUMULATED IN VISCERA AND RETINA

| METHOD USED | KIDNEYS /cases 2+3/ | GALL BLADDER /case 3/ | RETINA /case 2/ |
|---|---|---|---|
| SUDAN IV | – | 0 | – |
| SUDAN BLACK B | + | ++ | +++ |
| PAS | +++ | +++ | +++ |
| PfAS | – | – | – |
| ACETIC ACID CRESYL VIOLET | +++ | 0 | ++ |
| TOLUIDINE-BLUE STANDARD | ++ | 0 | 0 |
| FEYRTER'S "MOUNTING" METHOD | +++ | 0 | + |
| ORCIN-HYDROCHLORIC ACID | – | – | ± |
| COPPER-PHTHALOCYANIN | + | + | ++ |
| ALCIAN BLUE | ± | + | ± |
| OKAMOTO METH. | +++ | 0 | 0 |
| OKAMOTO METH. AFTER PYRIDINE | + | 0 | 0 |
| OKAMOTO METH. AFTER ETHER | + | 0 | 0 |
| COUPLED TETRAZONIUM | ++ | ++ | ++ |
| COUPLED TETRAZ. BENZOYL. | ++ | ++ | ++ |
| MILLON'S METH. | + | + | + |

\+ Faintly positive ++ Positive +++ Strongly positive ± Doubtful result – Negative 0 Test not done

TABLE IV

EFFECT OF DIFFERENT SOLVENTS ON STAINING PROPERTIES OF LIPID DEPOSITS

| SOLVENT | PERIODIC ACID SCHIFF | | | SUDAN BLACK B | | | METACHROMASIA | | |
|---|---|---|---|---|---|---|---|---|---|
| | NEURONES | MACROPHAGES | FREE DEPOSITS | NEURONES | MACROPHAGES | FREE DEPOSITS | NEURONES* | MACROPHAGES | FREE DEPOSITS |
| WATER | + | + | + | + | + | + | + | + | + |
| ETHER | + | + | + | + | + | + | + | + | + |
| ACETONE-cold | + | + | + | + | + | + | + | + | + |
| ACETONE-hot | + | + | + red | + red | + red | – | + red | + red | + red |
| ALCOHOL | + red | + red | – | + red | + red | – | – | – | – |
| PETROLEUM-ETHER | + | + | + red | + red | + red | – | 0 | 0 | 0 |
| PYRIDINE | + red | + red | – | + red | + red | – | – | – | – |
| CHLOROFORM-METHANOL | + red | + red | – | + red | + red | – | – | – | – |
| CHLOROFORM-ETHANOL | 0 | 0 | 0 | 0 | 0 | 0 | – | – | – |

\+ Staining of substance unimpaired +red Staining of substance reduced
– Staining of substance abolished 0 Test not done * Initially present in some nuclear groups only

lipids in granular cells of the white matter when stained with aniline dyes and with Sudan Black B. The effect of solvents on this birefringence is summarized in Table V. The accumulated material within neurones was not birefringent. In PAS stain, neither neurones nor macrophages showed birefringence. In the white matter birefringent sheaths were seen

TABLE V

EFFECT OF DIFFERENT SOLVENTS ON THE BIREFRIGENCE OF LIPID DEPOSITS

| SOLVENT | METACHROMASIA | | | SUDAN BLACK B | | | PERIODIC ACID SCHIFF | | |
|---|---|---|---|---|---|---|---|---|---|
| | NEURONES | MACROPHAGES | FREE DEPOSITS | NEURONES | MACROPHAGES | FREE DEPOSITS | NEURONES | MACROPHAGES | FREE DEPOSITS |
| WATER | – | + | + | – | + | + | – | – | – |
| ETHER | – | + | + | – | + | + | – | – | – |
| ACETONE-cold | – | + | + | – | + | + | – | – | – |
| ACETONE-hot | – | ± | – | – | ± | – | – | – | – |
| ALCOHOL | – | – | – | – | – | – | – | – | – |
| PETROLEUM-ETHER | – | – | – | – | + | – | – | – | – |
| CHLOROFORM-METHANOL | – | – | – | – | – | – | – | – | – |
| PYRIDINE | – | – | – | – | – | – | – | – | – |

\+ Birefrigence present  – Birefrigence absent  ± Birefrigence doubtful

surrounding axis cylinders which appeared to be devoid of myelin in ordinary methods. This phenomenon may be analogous to that described by Seitelberger (1960) in cases of Pelizaeus-Merzbacher disease, where demyelinated axis cylinders had a birefringent investment.

## BIOCHEMICAL STUDIES

Portions of the cerebral white matter and of the cerebral cortex were examined. Material from Case 2 was formalin fixed, while the portion of brain from Case 3 had been placed in the deep freeze at −20° C. and was dispatched by air and received still frozen. The lipid extracts were prepared using the technique of Folch *et al.* (1957*a*) employing a 2 : 1 chloroform-methanol (v/v) solvent mixture.

Water content, total phospholipid, sphingomyelin, total and free cholesterol were estimated as previously (Cumings, 1953). Total hexosamine and neuraminic acid were determined (Cumings, 1957), as were neutral cerebrosides (Radin *et al.*, 1955). Sulphatides were estimated by precipitating them as the barium salt using the technique of Radin *et al.* (1957) and the calculation was based on the formula of cerebron sulphuric acid as given by Folch *et al.* (1957*b*).

The results of these examinations on the brains of these 2 cases are given in Table VI. The figures obtained in Case 2 show in both the white matter and the cortex a very great loss of total phospholipids, a less severe loss of sphingomyelin and of cholesterol but with no significant amount of esterified cholesterol together with a normal water content. There is an apparently normal level of neuraminic acid (i.e. ganglioside) in the cerebral cortex but there is a definitely increased amount of total hexosamine in the white matter. The actual figure for sulphatides is normal, but, in view of the very gross loss of other lipids, must be considered as being abnormal.

In some respects there is less damage in Case 3 as evidenced biochemically. There is a small degree of loss of total phospholipids, less marked in the cortex than in the white matter. The same is true of the sphingomyelin

TABLE VI

CEREBRAL LIPIDS IN TWO OF THE CASES

| SUBSTANCE | Case 2. Age 5 Years | | Case 3. Age 3 Years | |
|---|---|---|---|---|
| | WHITE MATTER | CORTEX | WHITE MATTER | CORTEX |
| TOTAL PHOSPHOLIPIDS | 5.45 | 6.31 | 14.18 | 17.81 |
| SPHINGOMYELIN | 1.53 | 1.47 | 3.85 | 3.21 |
| TOTAL CHOLESTEROL | 6.08 | 5.47 | 6.84 | 6.14 |
| ESTERIFIED CHOLESTEROL | 0.22 | 0.15 | 0.20 | 0.23 |
| TOTAL HEXOSAMINE | 0.44 | | 0.57 | |
| NEURAMINIC ACID | | 0.18 | | 0.46 |
| NEUTRAL CEREBROSIDES | 2.3 | | 3.43 | |
| SULPHATIDES | 1.8 | | 6.30 | |
| WATER % | 77.8 | 81.0 | 75.6 | 82.6 |

Results in g./100 g. dry tissue.

and total cholesterol levels, and as in the other patient there is no significant amount of esterified cholesterol present. Neuraminic acid in the cortex is hardly raised above the normal level which at the age of this patient would be around 0·40 gramme per 100 grammes dry tissue (Cumings *et al.*, 1959). Total hexosamine in the white matter is very considerably increased (normal for age 0·30 gramme per 100 grammes dry tissue). Neutral cerebrosides are within the normal range but sulphatides in the white matter are very considerably increased, being nearly four times the normal figure for this age.

## DISCUSSION

Morphologically, the cases in our series appear to present the elements of two diseases, metachromatic leucodystrophy and familial amaurotic idiocy. The intensity of neuronal lipid storage and its distribution suggest a late infantile form of amaurotic idiocy in which the storage process never produces the degree of cellular distension seen in the infantile form (Seitelberger, *et al.*, 1957 and 1958; Diezel, 1960). The cerebellar lesions also support a diagnosis of the late infantile form. Although in none of our cases were retinal changes seen during life, the finding of pigmentary degeneration of the retina at autopsy on Case 2 is supportive evidence for this diagnosis. On the other hand, the diffuse demyelination of white matter in both cerebral and cerebellar hemispheres, accompanied by the presence of non-sudanophilic lipid deposits, classifies our cases as a form of diffuse sclerosis conforming, in general, to the type first described by Scholz (1925 and 1933). The outstanding morbid anatomical feature



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of Scholz's original cases, as well as of those subsequently described (Bielschowsky and Henneberg, 1928; van Bogaert and Scholz, 1932; van Bogaert and Bertrand, 1933; and others) was diffuse demyelination of the white matter with non-sudanophilic myelin breakdown products. The metachromasia present in our cases permits us to classify them as belonging to the metachromatic subgroup of leucodystrophy, as described by Einarson and Neel (1938), Wicke (1938), van Bogaert and Dewulf (1939), Brandberg and Sjövall (1940), Norman (1947), Brain and Greenfield (1950), Leslie (1952), Feigin (1954), Diezel and Richardson (1957), Wohlwill and Paine (1958), Hain and LaVeck (1958), Jervis (1958, 1960), Jefferson (1958), Peiffer (1959). Subsequent examination by Edgar (1955*b*), Hirsch and Peiffer (1955 and 1957) and by Diezel and Richardson (1957) showed that the majority of cases previously described as being of Scholz type had in fact, metachromatic properties. As in other cases of metachromatic leucodystrophy (Wicke, 1938; Norman, 1947; Brain and Greenfield, 1950; Leslie, 1952; Bertrand *et al.*, 1954; Einarson, 1954; Austin, 1957 and 1960; Jervis, 1958 and 1960; Hain and LaVeck, 1958) our cases had abnormal lipid deposits in some of the viscera. Like Brain and Greenfield (1950), Bertrand *et al.* (1954), and Diezel (1957), we observed metachromatic deposits in the peripheral nervous system.

The intensity of cortical destruction in our Cases 2 and 3 is unusual, and we are inclined to attribute it to combined involvement of neurones and subcortical nerve fibres. Oligodendroglia had almost completely disappeared from demyelinated areas and were much reduced in areas of partial demyelination; in a few, apparently well-myelinated areas oligodendroglia were reduced in number but this phenomenon to which Greenfield (1933) first drew attention, was not prominent.

The question arises whether our observations establish the presence in these cases of the lesions of both metachromatic leucodystrophy and amaurotic idiocy or whether we are here presented with an extreme degree of secondary demyelination in otherwise typical amaurotic idiocy. Some degree of demyelination is so common in amaurotic idiocy that cases without demyelination can be considered as rare. However in the published cases of familial amaurotic idiocy describing demyelination (Sachs, Bielschowski, Globus—quoted by Bérard-Badier, *et al.*, 1958; van Bogaert and Bertrand, 1933; Bird, 1948; Einarson, 1951; Leslie, 1952; Seitelberger, 1957 and 1958; Favarger and Wildi, 1957; Jervis, 1958; Benda and Melchior, 1958), the myelin breakdown products were sudanophilic. In the cases of Ostertag (1925), and Bérard-Badier *et al.* (1958), in addition to sudanophilic deposits, collections of "prelipids" were observed; however, even in these, the lipid deposits were not metachromatic. So far as we are aware, metachromatic lipid deposits have not been observed in the viscera in cases of amaurotic idiocy.

An alternative possibility is that the present cases are examples of metachromatic leucodystrophy in which neuronal changes are unusually advanced and widespread. However, despite the known variability of neuronal involvement, we have been unable to find in the literature cases of metachromatic leucodystrophy in which lipid storage involved neurones of all grey structures. We were not able to get a detailed pathological description of the case, mentioned by Einarson in his paper of 1951, in which a combination of the pathological changes of metachromatic leucodystrophy and amaurotic idiocy was mentioned. Moreover, in our cases metachromasia of the product stored in neurones was strictly confined to those nuclear groups in which it is commonly present in metachromatic leucodystrophy, while the Schaffer-Spielmeyer degeneration involved all neurones of the central nervous system.

Our cases, then, combine the complete pathological picture of both diseases. They occupy, from the morphological point of view, a central position between those lipidoses in which the leucodystrophic elements are most advanced (Ostertag, 1925; Bérard-Badier *et al.*, 1958) and those metachromatic leucodystrophies in which the intensity of the lipidotic features is greatest. Peiffer's (1959) case with cerebellar changes, and Einarson's (1951) and Leslie's (1952) cases with diffuse cortical storage degeneration most nearly approximate to ours.

Cerebellar changes are quite common in leucodystrophies (Poser, Dewulf and van Bogaert, 1957). Lesions of the cerebellar cortex were furthest advanced in one of Peiffer's (1959) cases where, in addition to intense atrophy of the granular layer, there were also Purkinje cell lesions. These changes, however, still fell short of those present in our cases.

We will discuss separately the results of our histochemical investigation of the deposits within neurones and within macrophages in the white matter.

First neurones: the negative results with Sudan IV enable us to rule out neutral fats and cholesterol esters as materials accumulated within neurones. The faint yellow-orange colour with Sudan IV in Case 1 is that seen with "prelipids." The strongly positive reaction with Sudan Black B (figs. 6 and 19) indicates the lipid nature of the accumulated material, and the relative resistance of this reaction to the activity of fat solvents suggests that the lipid is somehow bound into the cellular structure. On the basis of the Millon and of the Danielli reactions, we suppose that cellular proteins are the binding factor. The reduction in intensity of the Sudan Black B reaction following incubation in such fat solvents as absolute alcohol, petroleum ether, pyridine and a mixture of chloroform and methanol indicates the presence of some admixed lipid which is not bound with protein. The positive reaction with PAS shows that the stored material also contains a carbohydrate component. Simultaneous negative

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PfAS indicates that the PAS reaction is due to carbohydrate, not to unsaturated lipid. The striking parallelism in the decrease of staining intensity with Sudan Black B and with PAS after incubation in different fat solvents indicates a close linkage between the carbohydrate and lipid components of the accumulated material. The positive, although weak, reaction with Alcian blue indicates the presence of acidic groups in the stored material. Moreover, these substances give pink-red metachromasia in Feyrter's tartaric acid thionin. On the basis of these staining properties, we can define the accumulated material as an acid glycolipid, partially free, partially bound with protein. Of the two groups of glycolipids known to occur in the nervous system, namely gangliosides and cerebrosides, only gangliosides contain neuraminic acid. In our series, the Bial reaction for neuraminic acid was very weak in both paraffin and frozen sections. This result surprised us, as the material stored within neuronal cytoplasm in cases of familial amaurotic idiocy has been considered (Diezel, 1954*a* and *b;* Klenk, 1954; Seitelberger *et al.*, 1957) to belong to the gangliosides. More recently, however, Diezel (1960) has stated that, in the infantile form of amaurotic idiocy, the stored material is a neuraminic acid-free glycolipid which is considered by him to be a precursor of ganglioside; this substance, however, is readily soluble in fat solvents, not bound with protein and is confined to the infantile form of the disease, while our cases belong to the late infantile form. Theoretically we might suppose that our series represent a transitional form in which the accumulated glycolipids have formed the linkage with proteins but have not yet become attached to neuraminic acid. Alternatively, the faintness of the Bial reaction could be due to prolonged fixation in formalin (over one year), and/or to the presence of myelinogenic lipids in the white matter which probably inhibit the orcin-hydrochloric acid reaction. Several cases of morphologically typical amaurotic idiocy have been reported in which there was no increase of gangliosides but instead an accumulation of cerebrosides (Favarger and Wildi, 1957). In addition to the major stored material, we were able to establish the presence of some additional substances, amongst them, sphingomyelins; their presence was indicated by the persistent positivity of the Okamoto, Shimamoto and Ueda reaction after incubation in ether. The strongly positive original Okamoto reaction, resistant to pyridine but weakened by ether indicates that, in addition to sphingomyelins, some other phospholipid was stored. The material present within the neuronal cytoplasm of the dentate nuclei, globus pallidus, anterior horn cells of the spinal cord and pyramidal cells of the cerebral cortex differs from that in other neurones only in the occurrence of purple and brown metachromasia with acetic acid cresyl violet and tartaric acid thionin, other staining properties being identical with those in the remaining neurones. We interpret this finding as indicating the presence in these neuronal groups, of a lipid with the same solu-

bility and staining properties as that accumulated in the granular cells of the white matter; it is small in amount, the metachromasia never reaching the intensity seen in the granular cells.

The substances accumulated in the cytoplasm of the retinal ganglion cells have the same histochemical properties as those in neurones showing metachromasia. This is in accord with the observations of Cogan and his colleagues (1958).

White matter: The deposits in the white matter, both free and in macrophages, were negative in Sudan IV but positive with Sudan Black B (fig. 20); their PAS positivity was even more prominent than that of the neuronal deposits (fig. 21). This material is therefore also a glycolipid. Both the Millon and the Danielli reactions indicate a linkage of this material with protein when within macrophages but the extracellular granules were negative in both these tests. In contrast to the neuronal deposits, Bial's reaction was entirely negative in the white matter so that neuraminic acid must be considered absent in this situation. The occurrence of purple and of brown metachromasia in the white matter deposits was an even more distinctive property (fig. 22). The strongly positive Okamoto, Shimamoto and Ueda reaction of the large macrophages, disappearing completely after incubation in pyridine, indicates that the glycolipid which they contain is a cerebroside. The small macrophages showed minor differences in that their content gave a positive reaction with Alcian blue and remained slightly positive in the Okamoto reaction after pyridine and after ether; these properties indicate that there is some admixture of sphingomyelins and other phospholipids; positive staining with copper phthalocyanin supports this view.

The abnormal lipid deposits in the kidneys, liver and biliary tract had similar histochemical properties to those in the white matter.

In summary we may say that, while our investigation does not uniquely define the chemical nature of the substances accumulating in our cases, it does enable us to classify them. They are glycolipids, in great part bound with protein. Most of the material accumulated within neurones belongs to the gangliosides (despite the weak Bial reaction) or is formed by a substance intermediate between gangliosides and cerebrosides. The substances present in the white matter seem to be rather more close to cerebrosides. Because of their metachromasia, we can consider them as a sulphuric acid ester of cerebrosides (Jatzkewiz, 1958; Wislocki and Singer, 1950; Austin, 1957*a* and *b* and 1960). There are undoubtedly other substances present and the product stored in both neurones and granular cells in the white matter is not a homogeneous lipid but a mixture of lipids.

The histochemical studies reported by different authors have shown some differences in staining properties in cases of amaurotic idiocy. In meta-

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chromatic leucodystrophy histochemical variations have also been found. While these differences may depend in part on variations in histochemical technique, other more important factors probably operate. These include changes in the solubility of lipids under the influence of their linkage with cellular protein and the inhibition of the Bial reaction by myelin breakdown products. These differences may also be due to the different chemical structure and nature of the lipids accumulated in different cases. We do not feel, however, that these histochemical variations provide adequate reason to consider the conditions as distinct. Numerous biochemical investigations support this view and suggest the existence of mixed and transitional forms of storage disease.

Edgar (1956) has stressed that we cannot separate the pathophysiology of the component parts of the nerve cell, that is its pericarion and processes, and it seems reasonable to extend this principle to the myelin sheath which is so intimately related to the axis cylinder. The role of the axis cylinder in the normal production and maintenance of myelin is well known and it seems logical to suppose that similar or even identical enzyme systems manage lipid metabolism throughout the neurone-myelin sheath complex. Moreover the lipids involved are chemically similar, belonging to the sphingolipid group. In addition, Klenk's observations suggest that the myelin lipids may be derived from gangliosides. A genetically determined alteration of an enzyme system concerned in the metabolism of sphingolipids might produce changes in the whole group, leading to disease states in which the biochemical and histopathological features varied according to the position of the altered link in the enzyme system; it might for example result in alteration mainly of cellular lipids as in amaurotic idiocy or of myelin lipids as in metachromatic leucodystrophy. A mechanism of this type would account for deposits of lipid normally foreign to their site, e.g. sphingomyelins within the neuronal cytoplasm (Diezel, 1954 and 1960; Seitelberger, 1957) in the case of amaurotic idiocy or neuraminic acid and hexosamines in the white matter in metachromatic leucodystrophy (Brante, 1952; Edgar, 1955*b* and 1957*a* and *b;* Cumings, 1957 and 1960*a;* Svennerholm, 1957). Such a hypothesis also suggests the possible existence of intermediate forms of the diseases showing simultaneously alterations in both cellular and myelin sheath lipids. Our cases seem to us to occupy just such a position. The difference in histochemical properties of substances accumulated within neurones and granular cells of the white matter are a gauge of the difference between normal lipid components of the pericarion and of the myelin sheath.

The presence of strong brown metachromasia in apparently undamaged myelin sheaths in one of our cases (Case 2) supports Diezel's (1960) view that a metabolic abnormality in myelin sheaths precedes their destruction and the accumulation of abnormal products in granular cells. This evi-

dence of accumulation in both myelin sheaths and in phagocytes is the basis for the now accepted view that metachromatic leucodystrophy is rather a form of storage disease than a demyelinative disorder.

Edgar (1957) found a raised level of lipid hexosamine in the white matter of eleven cases, but the material had been stored in formalin over many years. A similar finding, except that total hexosamine was determined, has been found in a number of other cases (Cumings, 1957, 1960*a;* Black and Cumings, 1961; Tingey, 1959).

Austin (1957*a*) found metachromatic material in the urine, which was thought to be specific for the condition of metachromatic leucodystrophy and similar findings have been found by other workers (Cumings, 1960*b*, 1961). Jatzkewitz (1958, 1960) claimed to have isolated a cerebroside sulphuric acid ester in increased amounts in 2 cases, one of whom had been described clinically and histologically by Peiffer (1959) and biochemically by Cumings (1960*a*), and this increase was especially noticeable when the sulphatide fraction was related to the amount of the total sphingolipid present. Austin (1960) in 4 cases of metachromatic leucodystrophy found in the 3 brains examined by chemical methods an increase in cerebroside sulphuric acid esters. Hagberg *et al.* (1960) in 2 cases found very considerably raised levels of cerebroside sulphuric acid as well as increased amounts of hexosamine in the cerebral white matter. In 1960 one of us described 4 other cases verified by histological examination in all of whom raised levels of total hexosamine were found, while in 3 of these cases increased quantities of sulphatides were present (Cumings, 1961). Similar findings have also been recorded by other workers (Norman *et al.*, 1960; Black and Cumings, 1961). The 2 cases described here on which biochemical analysis of the brain was possible demonstrate the diagnostic lipid abnormalities of metachromatic leucodystrophy or sulphatide lipidosis, the name of the condition suggested by Austin (1960), for there was in these cases an increase of hexosamine and of sulphatide with loss of myelin lipids.

The chemical analysis revealed in Case 2 an apparent loss of gangliosides but in view of the very considerable reduction of other lipid compounds this low figure may not represent the true state of affairs. Case 3, however, did not show a significantly increased amount of ganglioside in the cortex as compared with a normal and the level is not as high as would be found in a patient of this age with amaurotic family idiocy.

The biochemical findings suggest that these 2 cases fall into the group of metachromatic leucodystrophy or sulphatide lipidosis and that the derangement is one in which there is some abnormality in one of the myelin components and this abnormality would appear less likely to be one resulting from an unusual demyelination than a consequence of a faulty formation of myelin in that a greater amount of a lipid material normally present is found in the cerebral white matter.

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The constancy of the neuronal groups involved in metachromatic storage is striking and implies some common factor in their metabolism differentiating them from other neurones. These groups are also subject to early and severe lipochrome degeneration and, while the mechanism of this is no doubt different, it probably reflects an analogous metabolic peculiarity.

The significance of changes in the viscera in the forms of lipidosis under discussion is controversial. Witte (1921), who found metachromatic deposits in various trunk organs in metachromatic leucodystrophy, suggested that they resulted from a generalized metabolic disturbance rather than a primarily cerebral disease. Austin holds a similar opinion. Other authors such as Brain and Greenfield, Norman, Leslie, Adams and Kubik (1952) who found metachromatic deposits only in some viscera with an excretory function, consider the process as primarily cerebral with secondary excretion of the abnormal products. Those cases in which visceral deposits were not found (van Bogaert and Dewulf, 1939) support the second possibility. In our cases the localization of abnormal deposits in the biliary and renal tracts, with histochemical properties identical to those of the white matter deposits, strongly incline us to this latter view, and we believe that the metachromatic nephrosis results from excretion of the cerebral products. The same holds true for the biliary tract. In this connexion it is noteworthy that a papilloma of the gallbladder, such as was present in our Case 3, was also found by Norman (1947) in one of his cases. The accumulation of macrophages filled with metachromatic substances in perivascular spaces in the brain suggests transport to the blood stream, while the metachromatic granulation in leucocytes, emphasized by Austin (1958), probably results from the well-known phagocytic properties of the granulocytes. Metachromatic deposits in the Kupffer cells of the liver can be similarly explained.

## Summary

(1) An account is given of 3 siblings with a progressive neurological disease in each of which there was histopathological evidence of both amaurotic idiocy and metachromatic leucodystrophy.

(2) The histochemical nature of the accumulated substances was investigated. Those found in the cytoplasm of neurones are considered to be mainly gangliosides or some glycolipids intermediate between gangliosides and cerebrosides. Those accumulated in the white matter are considered to be cerebrosides or cerebroside sulphuric acid esters. Evidence is given that there was an admixture of other lipids.

(3) Biochemical studies on tissue from 2 of the cases shows, in the white matter, an increase in hexosamine in both and an increase in sulphatides, absolute in one case and relative to the total lipid content in the other case. The neuraminic acid content of the cortex does not appear to be increased.

(4) It is suggested that a unitary, genetically determined abnormality of brain lipid metabolism underlies both conditions.

(5) Changes in the viscera, present in 2 of the cases, are believed to be secondary to the excretion of products of abnormal cerebral lipid metabolism.

ACKNOWLEDGMENTS

We are indebted to Dr. J. P. Robb who looked after these patients clinically and to Dr. G. C. McMillan in whose Department of Pathology the necropsies were performed. We are also indebted to Mr. H. Goodwin for technical help.

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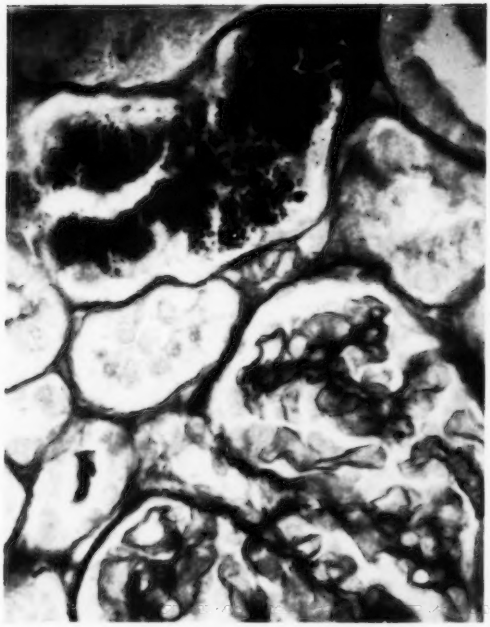

FIG. 2 (*Case* 2).—Kidney showing PAS positive granules in convoluted tubule. Paraffin. Periodic acid Schiff. ×550.

FIG. 3 (*Case* 2).—Kidney showing PAS positive casts in tubules. Paraffin. Periodic acid Schiff. ×350.

*To illustrate article by Miroslaw Mossakowski, Gordon Mathieson and John N. Cumings.*

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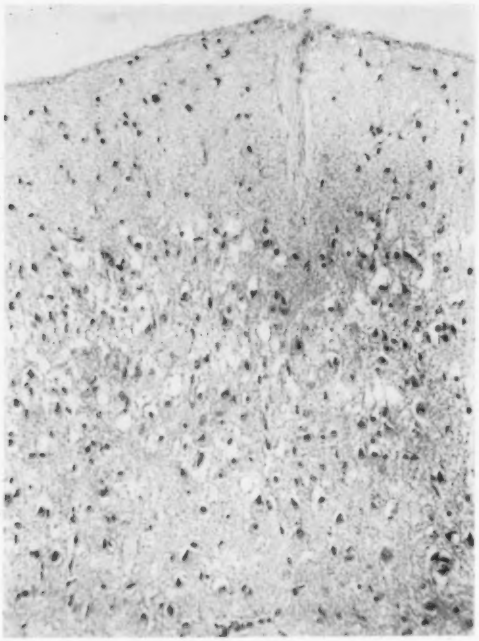

FIG. 4 (*Case* 2).—Frontal cortex showing neuronal loss and status spongiosus. Paraffin. Hæmatoxylin and eosin. ×130.

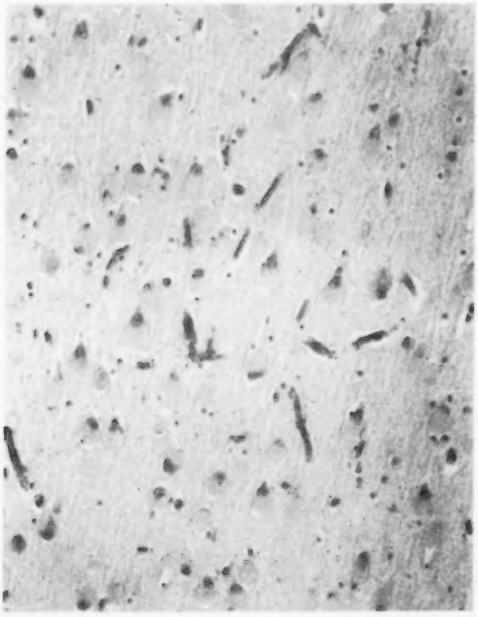

FIG. 5 (*Case* 2).—Hippocampal cortex showing universal distension of nerve cell bodies. Paraffin. Hæmatoxylin and eosin. ×250.

*To illustrate article by Miroslaw Mossakowski, Gordon Mathieson and John N. Cumings.*

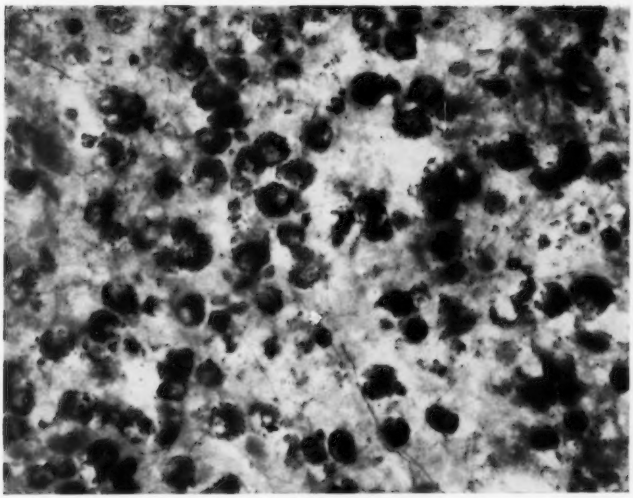

FIG. 6 (*Case* 2).—Frontal cortex showing abundant lipid accumulation in neuronal cytoplasm. Frozen section. Sudan Black B. ×300.

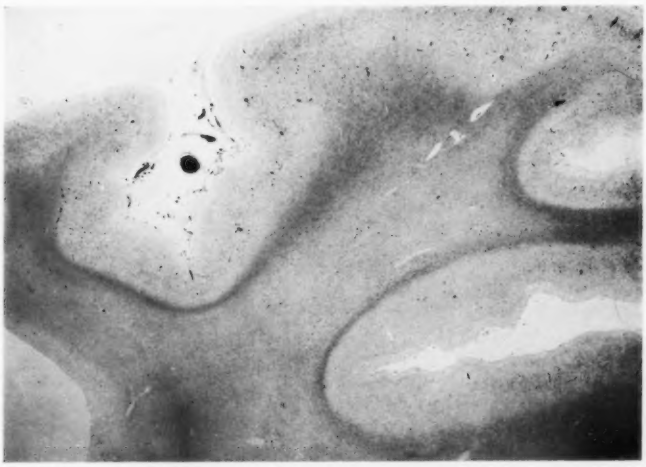

FIG. 7 (*Case* 2).—Frontal lobe. There is widespread demyelination but partial preservation in immediately subcortical regions where, in addition, macrophages contain material with the staining properties of myelin. Paraffin. Heidenhain's method for myelin. ×4.

*To illustrate article by Miroslaw Mossakowski, Gordon Mathieson and John N. Cumings.*

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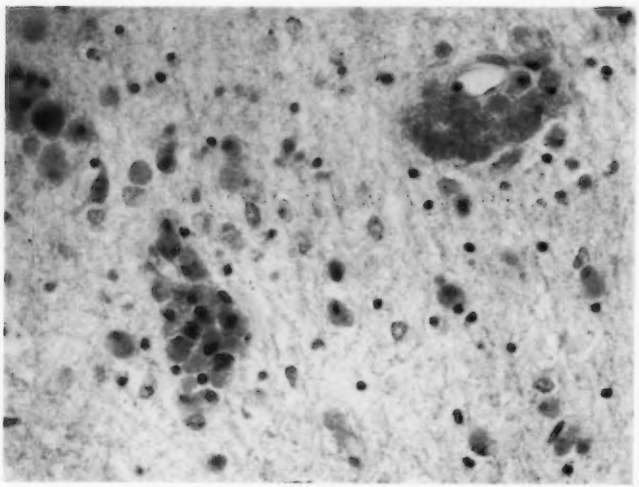

FIG. 8 (*Case* 2).—White matter of centrum ovale showing clusters of macrophages. Paraffin. Hæmatoxylin and eosin. ×420.

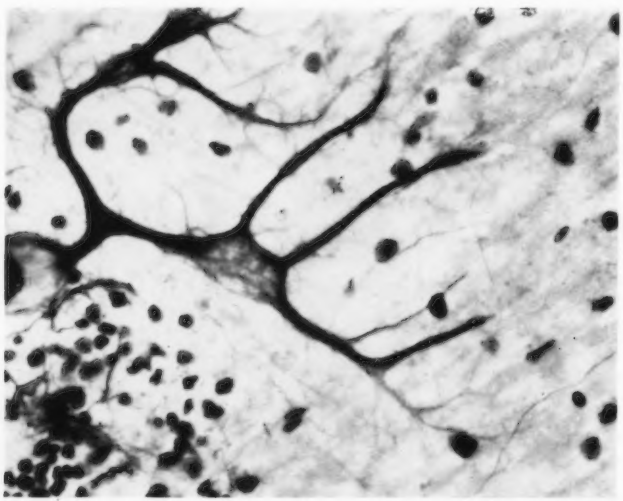

FIG. 9 (*Case* 2).—Cerebellar cortex. The Purkinje cell body is distended and ovoid. Swellings are present in the dendrites. Frozen section. Bielschowsky's method. ×600.

*To illustrate article by Miroslaw Mossakowski, Gordon Mathieson and John N. Cumings.*

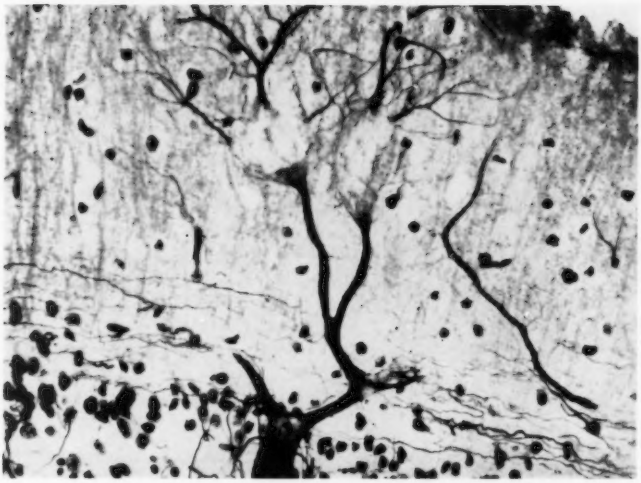

FIG. 10 (*Case* 2).—Cerebellar cortex. Another Purkinje cell showing ovoid swellings of two of its dendrites. Frozen section. Bielschowsky's method. ×600.

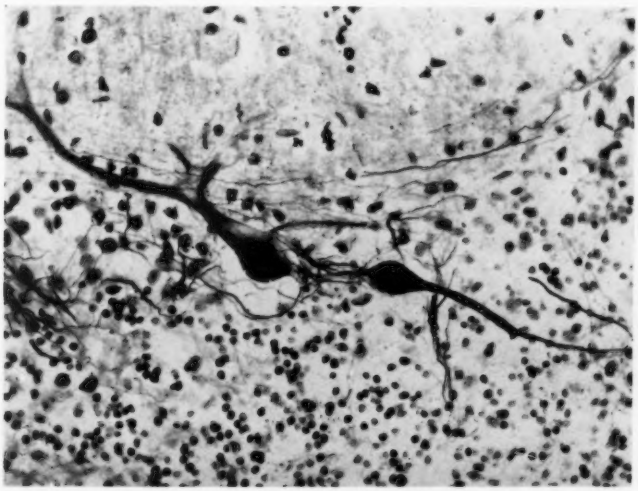

FIG. 11 (*Case* 2).—Cerebellar cortex showing torpedo-shaped deformity of Purkinje cell axon. Frozen section. Bielschowsky's method. ×380.

*To illustrate article by Miroslaw Mossakowski, Gordon Mathieson and John N. Cumings.*

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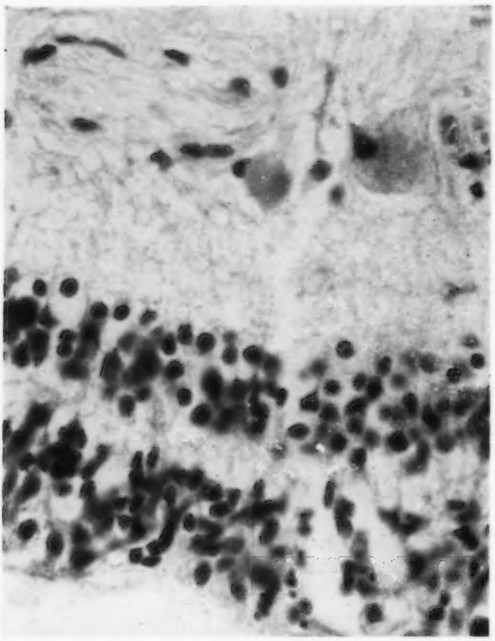

FIG. 12 (*Case* 2).—Retina. Two distended ganglion cells are seen in the upper part of the picture. The inner and outer nuclear layers are preserved. Paraffin. Hæmatoxylin and eosin. ×600.

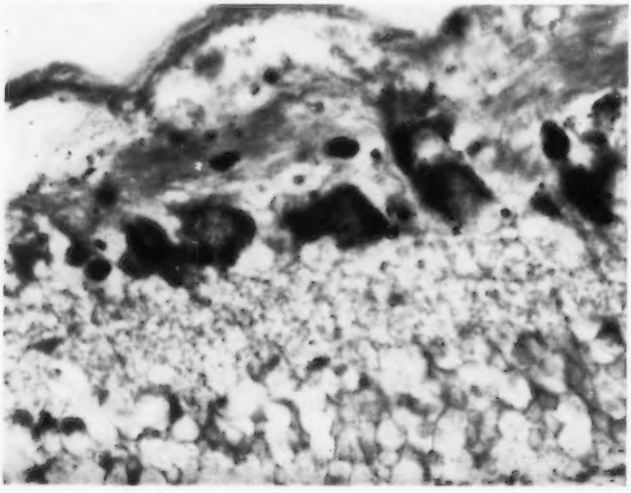

FIG. 13 (*Case* 2).—Retina showing lipid in ganglion cells. Scattered lipid granules are also present. Paraffin. Sudan Black B. ×520.

*To illustrate article by Miroslaw Mossakowski, Gordon Mathieson and John N. Cumings.*

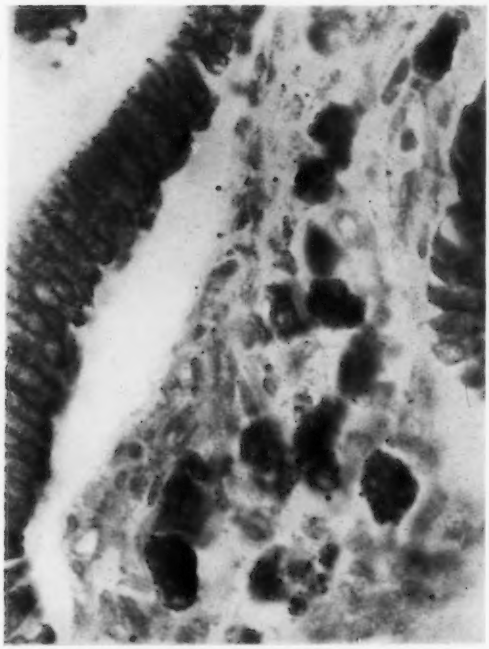

FIG. 14 (*Case* 3).—Gall-bladder. Lipid-laden macrophages are scattered in the mucosa. Paraffin. Sudan Black B. ×520.

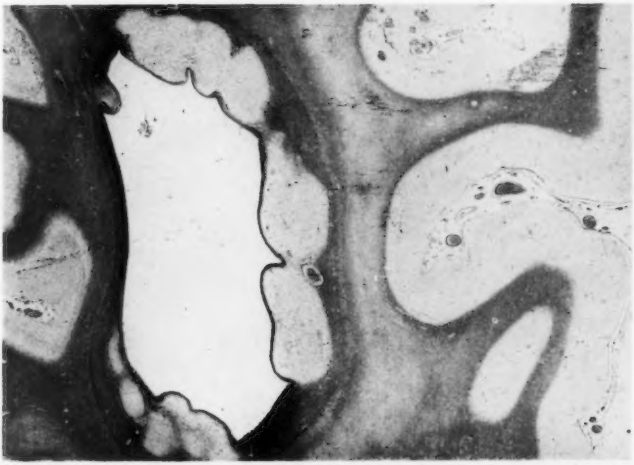

FIG. 15 (*Case* 3).—Right occipital lobe. The white matter is gliosed. Heterotopic foci of grey matter are present in the ventricular wall. Paraffin. Holzer's method. ×4.

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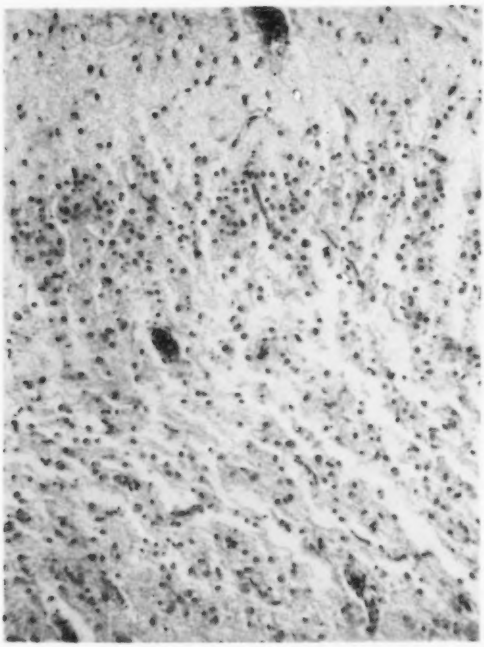

FIG. 16 (*Case* 3).—Occipital cortex showing destruction of architecture. The molecular layer at the top of the field is spared. Paraffin. Hæmatoxylin and eosin. ×130.

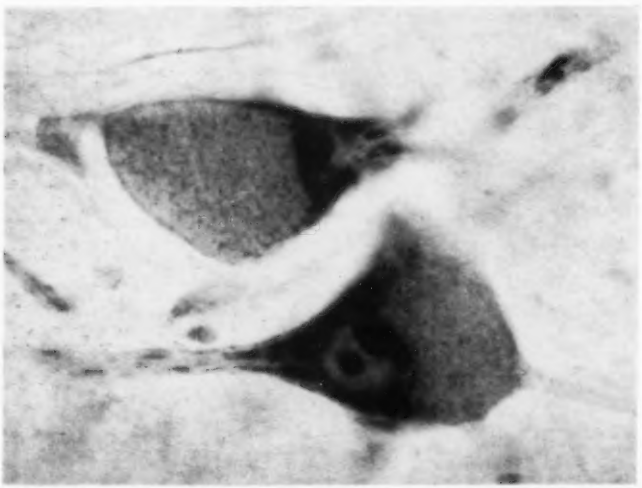

FIG. 17 (*Case* 3).—Hypoglossal nucleus. Two neurones showing distended, finely granular cytoplasm. The nucleus is displaced and Nissl substance crowded around it. Paraffin. Cresyl violet. ×780.

*To illustrate article by Miroslaw Mossakowski, Gordon Mathieson and John N. Cumings.*

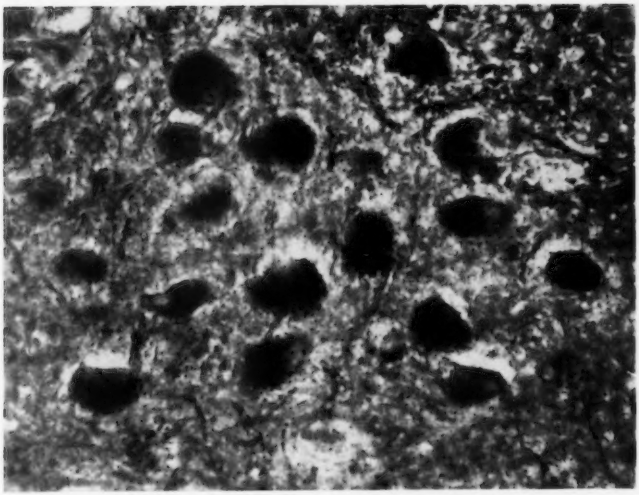

FIG. 18 (*Case* 3).—Dentate nucleus showing lipid content of neuronal cytoplasm. Frozen section. Sudan Black B. ×400.

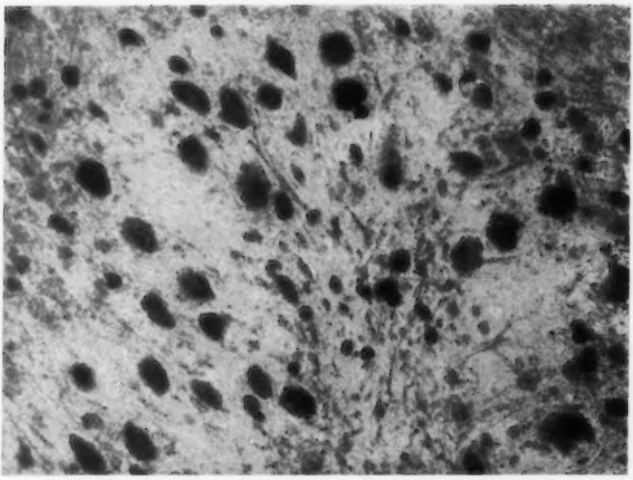

FIG. 19 (*Case* 2).—Dentate nucleus. Cytoplasmic deposits in the neurones show metachromasia (brown in section). Frozen section. Acetic acid cresyl violet. ×190.

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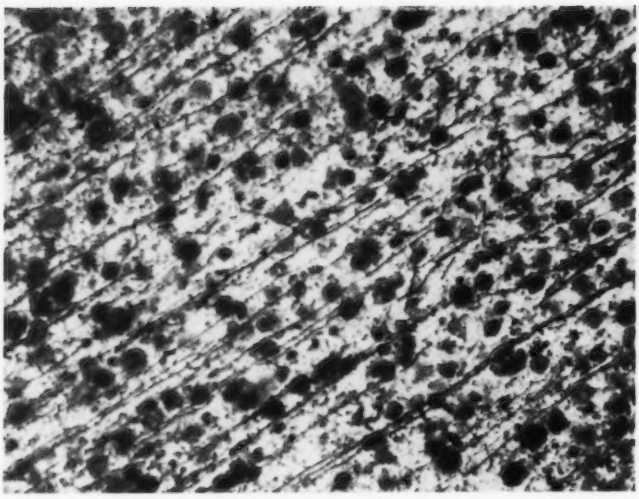

FIG. 20 (*Case* 2).—White matter of centrum ovale showing residual myelin sheaths and lipid-containing macrophages. Frozen section. Sudan Black B. ×160.

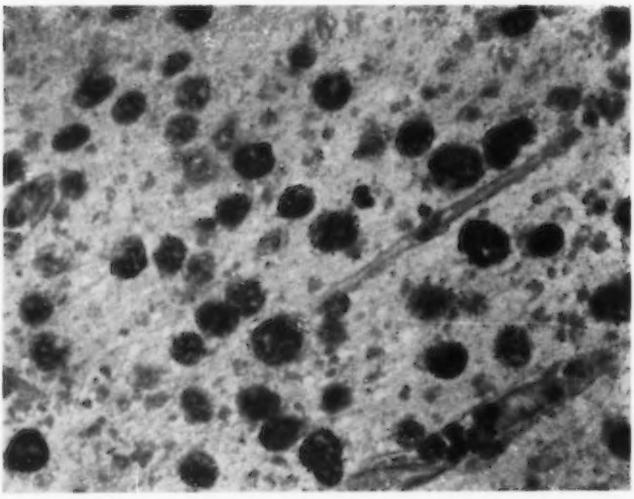

FIG. 21 (*Case* 3).—White matter of centrum ovale showing macrophages with PAS positive content. Paraffin. Periodic acid Schiff. ×300.

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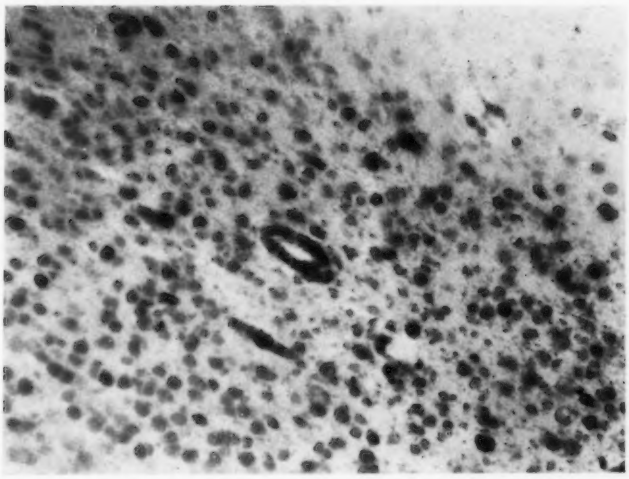

FIG. 22 (*Case* 2).—Frontal lobe. The white matter contains numerous macrophages with brown metachromatic material. Cerebral cortex at top right is free from metachromatic deposits. Frozen section. Acetic acid cresyl violet. ×130.

*To illustrate article by Miroslaw Mossakowski, Gordon Mathieson and John N. Cumings.*

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# MENINGIOMAS IN THE LATERAL VENTRICLES

BY

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## INTRODUCTION

MENINGIOMAS situated in the lateral ventricles, although generally considered to be extremely rare, are of particular clinical and pathological significance. Diagnosis is especially important because of the ease and excellent prognosis of surgical removal. Attempts to formulate a clinical syndrome have been unsuccessful; when localizing signs are present they do not differentiate lateral ventricular meningiomas from the group of posterior cerebral hemisphere tumours. Most of the previous studies of intraventricular meningiomas were published before the introduction of modern procedures of investigation. Other isolated case reports have either emphasized some unusual feature of the presentation or reintroduced the conclusions of earlier more comprehensive studies. The present study reviews the clinical features of lateral ventricular meningiomas and assesses the contribution of laboratory investigations in diagnosis. It formulates a picture suggestive of the diagnosis when the clinical presentation is combined with the results of investigations—which may in themselves be inconclusive.

Cushing and Eisenhardt (1938) differentiated *Choroidal Tumors of the Plexuses* which lie in the ventricles from *Lateral Tumors of the Velum Interpositum* which are at least partly embedded in the cerebral substance. They pointed out that this distinction was debatable because the large size of the tumours obscured precise definition of their origin. Few writers have adhered to this dichotomy and intraventricular meningiomas are treated as a unity in the present study.

In a series of 313 intracranial meningiomas Cushing and Eisenhardt (1938), found only 3 within the lateral ventricle. Dandy (1934) reported 15 benign encapsulated tumours of the lateral ventricle and calculated that these represented 0·75 per cent of all brain tumours; 3 of the cases

[1]Dr. Gassel is in receipt of Postgraduate Fellowship NBI-EP-BT- 482 from the National Institute of Neurological Diseases and Blindness, U.S. Public Health Service.

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were meningiomas. More recent tabulations have revealed a higher proportion of meningiomas within the lateral ventricles. Olivecrona (1947) found 18 in a series of 608 intracranial meningiomas, Ethelberg (1944) 11 of 187, and Huang and Araki (1954) 10 of 70. Wall (1954) collected 8 cases over a period of five years. Four of the cases in the present study (Cases 1, 3, 6 and 10) admitted to the National Hospital, Queen Square were incorporated in Wall's report. The higher contemporary frequency of lateral ventricular meningiomas is probably related to the routine preoperative investigation with air studies and the greater circumspection possible with modern methods of surgery.

This report is based on the finding of 11 lateral ventricular meningiomas in a review of 250 consecutive confirmed cases of meningioma admitted to the National Hospital, Queen Square in the eleven-year period 1948 to 1958.

## Case Histories

*Case* 1.—R. T., a 41-year-old man, complained of bi-frontal headaches for a six-month period prior to his admission under Dr. S. P. Meadows. The headaches were aggravated by coughing or stooping, spread to the occiput, and gradually became more severe in the following months. He had four attacks of excruciating headache lasting 15–45 minutes. In two of these episodes at the height of the headache he experienced a rotation of his environment and vomited. The vertigo lasted for 15–20 seconds during which time he had to support himself to avoid falling. For three to four months his main complaint, which caused him to seek medical advice, was of visual disturbance in the form of a "kink or zig-zag" at the point of fixation. The examination revealed bilateral papillœdema, and a slow irregular nystagmus on lateral gaze particularly to the left. There was mild ataxia of the limbs, and an unsteady gait especially on turning to the left. There were a few beats of ankle clonus bilaterally and extensor plantar responses. Joint position sense was impaired in the left hand and in both large toes.

*Investigations.*—The EEG showed a low voltage and less regular alpha rhythm on the left side. In the left anterior temporal region there were irregular 1–3 c/s waves, tending to occur in episodes. A space occupying lesion deep in the left hemisphere was suggested. Skull X-rays were normal. Ventriculography revealed widely dilated left temporal and occipital horns. Attempts to manipulate air into the body and anterior horn of the left lateral ventricle failed. The septum pellucidum was displaced to the right of the mid-line and the deviation was most marked anteriorly where it measured 1·4 cm. (figs. 1A and 1B, Plate LXVII). The appearance suggested a large space-occupying lesion in the region lateral to the body of the left ventricle and blocking the ventricle at this point. A burr-hole was next made in the left posterior frontal region; needling encountered a hard resistance at a depth of 4 cm. from the surface. A cyst was punctured which contained 10 c.c. of fluid under increased pressure. The cyst fluid contained 180 mg. per cent protein; no hooklets were seen on microscopic examination. Films after the cyst was tapped showed that the air was now entering the anterior horn of the left lateral ventricle. The displacement of the septum pellucidum was now considerably less marked (fig. 1C). Examination of the left ventricular fluid revealed a protein of 180 mg. per cent and 3 lymphoctyes; the right ventricular fluid contained 60 mg. per cent of protein and no cells. At exploratory operation an incision was made through the posterior part of the frontal lobe, A firm cystic mass was detected. It was smooth-walled and contained a few small

pieces of soft pink tumour tissue; biopsy showed the appearance of an ependymal cyst. A repeat air installation was later performed. Needling again revealed a cyst at 3 cm. depth from the cortex. Aspiration from the wall of the cyst failed because of its firmness. The impression was that the mass was movable. Air replacement showed a mass outlined posteriorly in the brow-down position. Some air was trapped anterior to the tumour (fig. 1D). There was less shift of the septum pellucidum and third ventricle than was previously noted. A space-occupying mass in the region of the trigone was diagnosed.

*Operation* was performed through a vertical incision in the parieto-occipital region. A yellow-grey knobbly tumour weighing 45 grammes was delivered. Its main vascular supply was from the choroid plexus. The histological picture was of a meningioma surrounded by a broad collagenous capsule and permeated by many thick bands of collagen. The cellular elements were mainly polygonal or elongated cells with rounded or elongated nuclei and a moderate amount of cytoplasm. The cells were in irregular clumps. Some areas had columnar types of cells arranged in parallel rows.

Following the operation the patient had severe global dysphasia, right hemianopia, right hemiplegia, and right-sided cortical sensory loss. In the next two weeks there was general improvement—least evident in the dysphasia which remained severe and most marked in the executive realm. Speech disturbance continued to improve in the following years but remained of moderate severity.

## COMMENT

The prominent false localizing signs of ataxia, nystagmus, and bilateral extensor plantar reflexes, in the absence of valid local evidence of the tumour, pointed to the erroneous clinical diagnosis of a posterior fossa tumour.

Intermittent symptoms, frequently at the height of the headache, pronounced influence of posture on the headache, or remissions in the course of illness were particularly common in lateral ventricular meningiomas. In this case there was the episodic complaint of vertigo at the height of the severe headache. Ventriculography revealed a remarkable decrease in the displacement of the septum pellucidum after evacuation of a "cyst"—the obstructed anterior horn. This horn filled with air on a subsequent instillation; and some air was trapped in the anterior horn in the brow-down position. This provides strong circumstantial evidence supporting the explanation of episodic symptoms on the basis of intermittent obstruction of a ventricular horn by the mobile tumour causing distension of the horn and resulting in brain displacement and distant effect on nervous structure.

*Case* 2.—A. B., a 42-year-old woman, complained of severe headache accompanied by vomiting three and a half years before admission to hospital under Sir Charles Symonds. The headaches were preceded by sudden blacking-out of vision to the left side which lasted for one to two minutes. They always started in the left temporal region, and lasted for two to three hours. The attacks occurred in the morning after rising. She had to recline with the pain and if she was able to fall asleep would awake free of pain. After two years the headaches ceased and she was free of complaints for one year. Six months before admission to hospital the headaches returned in the occipital region. They occurred on rising in the morning. She was able to avoid

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the headaches by getting out of bed slowly and assuming the erect posture with extreme caution. Straining aggravated the pain and caused sharp radiation to the vertex. The head was drawn over to the left side with the exacerbation of pain. In the same period the vision to the left side was impaired and she heard a swishing noise in the left ear. In the last weeks she had constant pins and needles in the left side of the tongue and both lips, fluctuating numbness in the left side of the face, and impairment of smell and taste. The patient was right handed. On examination there was papillœdema, right anosmia, and slight right proptosis. Visual acuity was 6/9 on the right and 6/18 on the left, and there was a partial left homonomous hemianopia slightly more marked in the lower quadrants. Hypalgesia was present in all three divisions of the left fifth cranial nerve and the corneal reflex was absent on the left.

*Investigations.*—Skull X-ray showed considerable enlargement and loss of definition of the sella. The pineal was displaced 1·6 cm. to the left of the mid-line. EEG revealed 2–5 c/s waves over a wide area on the right side but maximal in the posterior temporal region. A right carotid arteriogram showed elevation and stretching of the posterior portion of the Sylvian vessel group. The anterior cerebral artery was displaced 1 cm. to the left of the mid-line. The terminal portion of the right posterior cerebral artery was elevated. No pathological vessels were seen. The appearances were those of a large space-occupying lesion in the parieto-temporo-occipital region, probably a glioma.

*Operation.*—At fronto-parietal craniotomy a biopsy was taken and revealed no neoplastic tissue. A decompression was performed.

The patient's general condition improved after the decompression and she was discharged from hospital. She had subsiding papillœdema and a tendency to drag her left leg. Two years after discharge the headaches returned, and in the next six months they were present every morning on awakening and associated with vomiting. Straining made her legs feel weak, caused pins and needles in her face, and made her eyes water. She also experienced unpleasant smells lasting for a few minutes. On rare occasions she had "gone out of herself" and became lost in familiar surroundings.

On readmission there was moderate mental deterioration. Her head was tilted to the left. The temporal decompression site was tense. She tended to ignore the left half of the body. There was slight swelling and consecutive atrophy of the optic papillæ. A left homonomous hemianopia with macular sparing was found. There was diminished sensation to pin-prick in all three divisions of the left fifth cranial nerve. A mild left hemiplegia and cortical sensory loss was present on the left side of the body. Skull X-rays were unchanged, and the EEG alterations were believed to be secondary to the decompression. The clinical impression was unchanged—a deep right posterior hemisphere glioma. A biopsy was taken through a posterior parietal burr-hole. It revealed a meningioma formed of whorls and fascicles of rounded and elongated cells with a large amount of cytoplasm. At ventriculography the septum pellucidum was angulated and shifted to the left of the mid-line 0·5 cm. anteriorly and 1 cm. posteriorly. The right lateral ventricle was displaced under the falx and the posterior end of the third ventricle was markedly angulated. In the brow-down position a large quantity of air was trapped in the widely dilated temporal horn (fig. 2). The appearances suggested an intraventricular space-occupying mass in the region of the right trigone.

Uneventful operative removal of a 246 gramme intraventricular meningioma was carried out through a vertical incision in the right posterior parieto-temporal region. Post-operatively there was a slight transient increase in the left hemiparesis; the hemianopia remained unchanged. In the following years there was little alteration in her condition.

## Comment

Periodic phenomena, largely correlated with postural changes, were striking. These are exemplified by the headaches and vomiting occurring in the morning after rising, preceded by blacking-out of vision to the left side, relieved by reclining, prevented by carefully assuming the erect posture, and accompanied by twisting of the head to the left side. The fluctuating paræsthesiæ of the face and the weakness of the legs on straining are similar in character to the above episodes. Ventriculography showed trapping of a large quantity of air in the grossly dilated ipsilateral temporal horn in the brow-down position.

The location of the tumour deep in the posterior half of the brain is an unusual one for a benign neoplasm. It made the likely clinical diagnosis one of glioma—a conclusion supported by the arteriographic findings. This diagnosis resulted in the postponement of the air studies and delay in the surgical excision of the tumour.

*Case* 3.—J. M., a 15-year-old girl, developed daily frontal headaches present on awakening for nine months prior to admission to hospital under Dr. MacDonald Critchley. Seven months before entering hospital she experienced variable weakness in the left hand and altered sensation in her left forearm and hand which she was unable to describe adequately. Two months later she complained of a twitching feeling in the right side of the face which extended from the eye to the chin but did not involve the nose or lips. It occasionally occurred when washing her face, but was not brought on by otherwise touching the face or chewing. During the attacks of right facial paræsthesia the weakness of the left arm was accentuated. A few days before entering hospital the patient had a severe attack of this type with associated headache and vomiting and was observed by her mother to have a vacant look and to be unable to speak. In the last few months she had transient weakness of the left foot. She was right handed. Examination revealed a slight mental deterioration, and chronic papillœdema. Campimetry showed a left homonymous hemianopia with macular sparing and peripheral constriction of the visual fields. There was a moderate left hemiplegia and gross left-sided cortical sensory loss.

*Investigations.*—Skull X-ray showed changes consistent with raised intracranial pressure. EEG revealed 1–3 c/s waves of moderately high voltage and variable phase relationships in the right temporo-parietal region and bursts of rhythmic 3 c/s waves in the right frontal region, which suggested a tumour in the right temporal parietal area, at least in part sub-cortical. Ventriculography showed the septum pellucidum and third ventricle displaced 1·5 cm. to the left of the mid-line. A large tumour in the right trigonal region was almost completely outlined by air. The anterior end of the right temporal horn was grossly dilated and emptied slowly of air in the brow-down position due to obstruction of its posterior part by the tumour (figs. 3A and 3B). Laboratory examination of the right ventricular C.S.F. revealed a protein of 140 mg. per cent with 56,000 R.B.C. and 100 W.B.C. per c.mm.; left ventricular fluid had a protein of 45 mg. per cent with 7,500 R.B.C. and 7 W.B.C. per c.mm.

*Operation.*—Through a curved parieto-temporal incision a meningioma weighing over 160 grammes was uneventfully removed. Histologically it was composed of thin elongated cells, many of which formed whorls. There were scattered collections of larger cells with large oval or rounded nuclei and ill-defined cytoplasm. A distinct

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capsule surrounded the tumour and many well-formed blood vessels and numerous collagen fibres permeated the tumour.

Following the operation there was rapid improvement in the patient's condition and three weeks post-operatively there were no motor signs and only moderate left-sided cortical sensory loss; the left homonymous hemianopia was unchanged.

## Comment

The intermittent weakness of the left arm and leg together with episodic paræsthesia of the right face are recurrent phenomena of the type described in previous cases. The facial paræsthesia sometimes occurred when washing (and thus bending forward) but not by otherwise touching the face or chewing, and was associated with headache and vomiting on one occasion. Ventriculography demonstrated partial occlusion of the widely dilated temporal horn in the brow-down position.

This was one of the few cases in which clinical examination effectively lateralized the tumour.

*Case* 4.—S. P., a 21-year-old Indian woman, was admitted under the care of Dr. Denis Brinton. Six months previously she had developed mild frontal headaches when in the seventh month of her second pregnancy. Two months later, after an uncomplicated delivery, the headaches increased in severity and radiated to the occiput. They were aggravated by straining or stooping. Transient blurring of vision was noted, frequently at the height of a headache; these blurrings continued although the headaches diminished. She had two attacks in which she felt a twisting and numb feeling within the left arm lasting for two minutes; in the second attack the left side of the face was also involved. Both of these episodes occurred at the height of a headache; there was no movement of the affected parts or impairment of consciousness. She had a few episodes of double vision lasting for seconds; and in the months before admission she noticed a buzzing in both ears. On admission the only abnormal findings were severe papillœdema with enlargement of the blind spots on visual field examination and a larger left pupil.

*Investigations.*—Skull X-rays showed decalcification of the dorsum sellæ from raised intracranial pressure. Unusually large and tortuous vascular markings were seen in both parietal regions. EEG revealed irregular slow activity which tended to occur in bursts in the left fronto-temporal region.

The clinical impression was that this might be a case of post-partum toxic hydrocephalus and it was decided to observe the patient closely before further investigation. In the following weeks there was pronounced improvement in the appearance of the fundi which then revealed no swelling. The patient was discharged with the tentative diagnosis of cerebral thrombophlebitis.

After discharge her headaches were infrequent and her eyesight improved. One year later severe headaches suddenly recurred. They were continuous for a three-week period prior to readmission. On examination the patient was lethargic and apathetic. There was slight pallor and œdema of the optic discs. A right homonomous visual field attention defect was suggested but co-operation was poor. There was slight right-sided weakness. Ventriculography showed shift of the septem pellucidum to the right of the mid-line 1 cm. anteriorly and 2 cm. posteriorly. The posterior end of the left lateral ventricle was elevated and displaced inwards. Air was trapped anterior to the tumour in the brow-down position and the trapped air outlined a convex border to the mass (fig. 4). A large parieto-occipital space occupying mass was diagnosed.

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*Operation.*—A large rounded freely mobile tumour was found arising from the choroid plexus in the trigone of the left lateral ventricle and extending into the body and temporal horn of this ventricle. There was great dilatation of the left temporal horn. The tumour, which weighed 44 grammes, was a meningioma formed of whorls and bundles of elongated cells permeated by strands of collagen.

Immediately after the operation the patient was severely dysphasic. There was slight right-sided weakness and an incomplete homonomous hemianopia. In the following weeks there was rapid improvement in speech. One and a half years post-operatively there was no evidence of dysphasia; vision was 6/9 bilaterally; and a partial right homonomous visual field defect was the only abnormality.

## Comment

In the first admission to hospital there were no clinical features to localize the tumour. The attacks of sensory disturbance in the left arm and face at the height of the headache were misleading. The clinical impression of post-partum toxic hydrocephalus was supported by the disappearance of the papillœdema and by the general improvement during admission.

Periodic symptoms are illustrated by the well documented and remarkable remission in the course of illness, intermittent diplopia, and the episodic left-sided sensory disturbance at the height of the headache. There was great dilatation of the left temporal horn on ventriculography and the freely mobile tumour trapped islands of air in this horn on changes in head posture.

*Case* 5.—C. D., a 24-year-old man, complained of dull bi-frontal headaches with an occasional stabbing pain behind the right eye six months before admission to hospital under Dr. William Gooddy. The headaches spread to the occiput and increased in severity, even waking him from sleep. They occurred daily and lasted from one to five hours. He usually obtained immediate relief if he bent the head forward and began to sweat. The sweating was essential for the process to be effective and other head positions had no effect. He was frequently nauseated with the headaches but never vomited. In the two months previous to admission his vision gradually deteriorated and he had frequent obscurations of vision unaffected by the position of the head. He also had urgency and frequency of micturition with occasional incontinence. When he reclined on his back his arms felt "dead-like," but there was no tingling in his fingers or similar sensation in the lower limbs. On examination there was abnormal prominence of the eyes, bilateral anosmia, and moderate papillœdema. The visual acuity was 6/12 on the right and 6/60 on the left. The visual fields were constricted and there was a right nasal field defect. The left pupil was smaller than the right. There was a bilateral external rectus palsy. The right lower face was slightly flattened. There was a fine tremor of the fingers of the right hand and clumsiness in the finger-nose and heel-knee test of the right side. The deep tendon reflexes on the right side were sluggish.

*Investigations.*—Skull X-rays revealed gross destruction in the region of the pituitary fossa with the anterior clinoid processes undercut to the limits of the sphenoidal air sinus and the posterior clinoids almost entirely destroyed. The skull vault showed deepened convolutional markings. The appearances suggested an expanding lesion arising in the neighbourhood of the pituitary fossa—possibly a pituitary adenoma. The EEG revealed considerable 4–7 c/s activity widely dis-



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tributed on the left side but most pronounced in the temporal region where it was of higher voltage, aggregated into short runs of rhythmic 5 c/s activity, and sometimes focal. The record was interpreted as indicating a tumour deep in the left temporal lobe. At ventriculography the ventricular system was moderately dilated and the left temporal horn widely dilated. The septum pellucidum was displaced to the right 1 cm. anteriorly and 2 cm. posteriorly. The third ventricle was similarly displaced to the right more marked posteriorly, and there was gross dilatation of the anterior part of the third ventricle while the posterior part was flattened (figs. 5A and 5B). A large filling defect almost blocked the trigone of the left lateral ventricle and encroached on the posterior part of the temporal horn. There was some trapping of air in the dilated temporal horn in the brow-up position. The appearances were those of a space-occupying mass in the trigone of the left lateral ventricle.

*At operation* there was uneventful removal of a 52 gramme intraventricular meningioma which was anchored by a wide base in the anterior trigonal region. Histologically the tumour was formed of whorls and columns of rounded and elongated cells with vesicular nuclei, relatively large amounts of cytoplasm, and indistinct cell margins. Bands of collagen separated the cellular elements, and the tumour periphery was covered in large part by a thick collagen capsule. There were many blood vessels supplying the tumour.

Post-operatively the patient was dysphasic and had a right hemiparesis and right-sided cortical sensory loss. The vision remained grossly impaired and was compromised further by a post-operative right homonomous hemianopia. In the following months there was gradual improvement in speech function and in the use of the right extremities. The vision deteriorated still further with the development of secondary optic atrophy and remained his major disability.

### Comment

The prominent false localizing signs point to the diagnosis of a posterior fossa tumour, whereas the skull X-rays showed remarkable destruction of the pituitary fossa suggestive of an intrasellar neoplasm.

In this case there was postural relief of headache (only on bending forward and after sweating) and a peculiar sensation in the arms on reclining. Ventriculography showed trapping of air in the grossly dilated left temporal horn on changes in head posture.

*Case* 6.—M. E., a 51-year-old woman, complained of bi-frontal headaches for one year before admission under Sir Charles Symonds. The headaches were generally present on awakening and gradually disappeared in the following few hours; they rarely recurred in the evening. The pain was not aggravated by straining or bending, but was relieved by lying down. In the last six weeks there was slowly increasing weakness of the right arm and leg. She was right-handed. Examination revealed mild mental deterioration and mild nominal dysphasia. Papillœdema was present. Visual acuity was 6/24 bilaterally, and a right homonymous visual attention defect was elicited on bilateral stimulation. There was a slight right hemiparesis and right-sided cortical sensory loss.

*Investigations.*—Skull X-ray showed erosion of the dorsum sellæ and enlargement of the pituitary fossa from raised intracranial pressure. EEG revealed moderate voltage 1–4 c/s activity in the left mid-temporal region. At ventriculography a left parieto-occipital needle probe encountered an irregular resistance deep in the hemisphere; a biopsy revealed a meningioma. Air replacement showed the septum pellucidum displaced 1 cm. to the right of the mid-line. The right lateral ventricle was

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grossly dilated; dilatation was much less pronounced on the left side. The anterior horn was poorly filled on the left side and in the brow-down position air was trapped in the anterior horn outlining the tumour anteriorly and medially. There was an enormous filling defect in the lateral ventricle which extended posteriorly to within 2 cm. of the occipital horn and anteriorly to the region of the foramen of Monro (figs. 6A and 6B). A large mass pressing upon the ventricle was diagnosed.

*Operation.*—A 3 cm. vertical incision was made in the left parietal cortex. A purplish vascular growth was found within the ventricle. It did not separate easily and appeared to be invading the surrounding brain tissue. The tumour was partially removed. It was a meningioma composed of solid masses of large polyhedral cells with indefinite cell margins; some cells were multi-nuclear and hyperchromatic and a few contained mitotic figures. Smaller cells with dark elongated nuclei were present in regions of the tumour which were degenerating; these cells tended to form whorls. Numerous fine thin-walled blood vessels permeated the tumour. Reticulin was present in the walls of the blood vessels and outlined some of the cells. There was a clear line of demarcation from normal cerebral tissue.

The operation slightly aggravated all the previously recorded defects. The patient was more mentally retarded and lacked insight. A course of radiotherapy was prescribed. Two years later the onset of nausea and vomiting made a further operation necessary. There was complete removal of a 30 gramme tumour which separated freely and was attached to the choroid plexus. Post-operatively the patient was severely dysphasic and there was a severe right hemiplegia and right-sided cortical sensory loss. In the next six months there was much improvement in the dysphasia and in the right-sided weakness but the cortical sensory loss remained severe. The patient's condition varied in the next three years but for a large part of the time she was able to care for herself and manage her household.

## COMMENT

The locality of the tumour was clear on clinical criteria—not the specific intraventricular position. There was a history of relief of headache on reclining. Ventriculography showed an enormous filling defect of the left lateral ventricle which was interpreted as a mass pressing on the ventricle; however, the trapping of air in the anterior horn in the brow-down position is diagnostic of an intraventricular tumour.

*Case* 7.—J. T., a 12-year-old girl, began to have attacks of blankness twenty months previous to admission under Sir Charles Symonds. The attacks lasted from a few seconds to 15 minutes. She had no warning or subsequent memory of them. Some times she smacked her lips and mumbled unintelligibly. In the longer attacks she might search around the room or carry out other highly organized but purposeless acts. She was right-handed. The only abnormal physical finding was moderate papillœdema.

*Investigations.*—Skull X-rays showed slight diastasis of the coronal suture and some decalcification of the sella. A diffusely calcified lesion measuring 5 × 8 cm. occupied almost the entire left temporal region (figs. 7A and 7B). The appearances suggested a benign type of glioma or possibly an ependymoma. EEG revealed continuous irregular slow activity with many sharp waves and some spikes in the left anterior and mid-temporal regions, and a diminished alpha rhythm on the left. At ventriculography only the right lateral ventricle filled. The septum pellucidum was displaced 0·5 cm. to the right of the mid-line.

It was thought that the patient had a large glioma and that operative removal

would result in a severe disability; radiotherapy was suggested. After re-appraisal it was decided to excise the tumour sub-totally as an initial procedure to prevent the development of secondary optic atrophy.

*Operation.*—The tumour proved to be a large meningioma vastly expanding the temporal lobe and leaving only a shell of brain less than 1 cm. in thickness. It was separated with ease and was completely removed. The only incision into the brain in the process of removal was the original one of 6 cm. length in the line of the superior temporal convolution; no brain was removed. Histological examination revealed that the growth was formed of clusters and bundles of cells with slender elongated nuclei and a small amount of cytoplasm. Some of the bundles were interlaced and the cells tended to lie in concentric arrangement. Many blood vessels were found in the tumour and reticulin was present around the blood vessels and between the individual cells. Calcospherites occurred within the growth and in the contiguous cerebral tissue. These were the appearances of a hæmangio-endothelioma.

Post-operatively there was no evidence of speech defect and the only abnormal finding on discharge from hospital two weeks later was a partial upper right homonomous quadrantic visual field defect.

## Comment

The clinical presentation was dominated by temporal lobe epilepsy and this was the only patient who had definite pre-operative epileptic attacks. The tumour filled the temporal horn leaving only a thin covering shell of brain.

Once again the clinical impression was of a large deeply situated glioma and this was supported by the straight X-ray changes. Ventriculography contributed little to the diagnosis. Partial excision of the tumour was decided upon only after some hesitation in view of its location in the dominant hemisphere and the likelihood of severe post-operative disability. The tumour was removed easily and with excellent results.

*Case* 8.—Eleven months previous to admission under Dr. E. A. Carmichael, J. E., a 30-year-old Maltese man, had a febrile illness lasting a few days. One month later he began to have attacks of dimness of vision. They occurred at any time of the day and were sometimes precipitated by bending. Four months after the onset of illness he was observed to have bilateral papillœdema without other abnormal physical signs. The lumbar C.S.F. pressure was 300 mm. A diagnosis of "serous meningitis secondary to brucellosis" was made and regular lumbar punctures were begun. They were continued for six months at intervals of never more than a week; the C.S.F. pressure varied between 240–300 mm. On examination the patient appeared to be in robust health, but with bilateral papillœdema and some enlargement of the blind spots of the visual fields.

*Investigations.*—Skull X-rays showed some decalcification of the posterior clinoid processes consistent with the diagnosis of raised intracranial pressure. EEG revealed a focus of 5 c/s waves and occasional 2–3 c/s waves arising in the left occipito-temporal region. At ventriculography a right posterior parietal burr-hole was made. Air filled only the right lateral ventricle; a small amount was manipulated into the third ventricle with difficulty. Anteriorly there was a 0·5 cm. shift of the septum pellucidum to the right of the mid-line and also a shift and angulation of the third ventricle; posteriorly the displacement was more pronounced measuring 2 cm. A second burr-hole was made in the left posterior parietal region and air replacement outlined a

large space occupying mass within the trigone of the left lateral ventricle (figs. 8A and 8B). The left temporal horn was not demonstrated.

*Operation.*—The intracranial tension was extremely high and little reduction in pressure occurred on needling the ventricle. Drainage was instituted with the intention of performing the operation in two stages. However, after three days the patient suddenly lost consciousness and died. Post-mortem examination showed flattening of the cerebral convolutions. There was a large meningioma arising from the choroid plexus of the left lateral ventricle. The left temporal horn was widely dilated. The hippocampal gyri were herniated through the tenotrium and a marked cerebellar pressure cone was present. Histologically the tumour was formed of bundles and whorls of elongated cells. It was surrounded by a fibrous tissue capsule.

## COMMENT

The paucity of signs of local disease in these cases with large tumours in the posterior part of the dominant cerebral hemisphere is remarkable. In this case symptoms of raised intracranial pressure were present for eleven months prior to admission to hospital. The lateral ventricular region is one of the unusual "silent areas" of the brain.

The left temporal horn, which did not fill with air at ventriculography, was found to be widely dilated at post-mortem examination. The dilatation resulted from obstruction to outflow by the large intraventricular tumour.

*Case* 9.—P. H., a 60-year-old male patient of Mr. Wylie McKissock, was transported to the hospital in a confused condition; the history was obtained from an accompanying letter. He had been admitted to another hospital two weeks previously with a story of a progressive left hemiplegia of three months' duration, headaches unassociated with nausea or vomiting for two weeks, and recent poor appetite. On examination he was reported as conscious and orientated but drowsy. The optic fundi were normal. There was a spastic left hemiplegia and mild sensory impairment in the left extremities. Skull X-ray revealed the calcified pineal gland displaced to the left of the mid-line. At lumbar puncture the pressure was 200 mm. of water and the C.S.F. contained 50 mg. per cent of protein and 3 cells, but was otherwise normal. In the immediate interval before referral the patient suddenly became very drowsy. On examination the patient was drowsy and confused. There was neck stiffness, a positive Kernig's sign, and a severe spastic left hemiplegia.

*Investigations.*—At ventriculography the intracranial pressure was elevated. The ventricles were moderately dilated. The septum pellucidum was upright and shifted 1 cm. to the left of the mid-line. There was a mass within the right lateral ventricle which appeared cystic and contained loculated air spaces (fig. 9). A biopsy was taken through a trephine hole in the right mid-parietal region. A pale firm tumour was encountered within a cystic cavity. Histologically the tumour was composed of interlacing bundles of cells with a tendency to whorl formation. Some nuclei were elongated and there were many cells with pleomorphism and mitoses, and many giant cells. Blood vessels were numerous and there were many areas of necrosis. A few psammoma granules were found. Most fibres stained positively with reticulin stain and red with Van Gieson; PAH did not stain the fibres. The tumour had the features of a sarcoma and was diagnosed as a malignant meningioma.

The patient's condition continued to deteriorate and he died one day after the biopsy. Post-mortem examination revealed the brain to be swollen. A large well-

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demarcated tumour was found in the body of the right lateral ventricle and extending anteriorly through the foramen of Monro and slightly into the third ventricle. The tumour was very firm and had a smooth surface. It appeared to have arisen in the neighbourhood of the ventricular wall and it displaced the internal capsule and basal ganglia laterally and the thalamus and hypothalamus downwards. There was bilateral uncinate herniation and a small amount of foraminal herniation of the cerebellar tonsils. Section of the pons showed scattered hæmorrhages in its upper half.

### Comment

The essential extracerebral nature of lateral ventricle meningiomas, which is at the basis of their unique character, is illustrated by the extension of the mass through the foramen of Monro and into the third ventricle in this case.

*Case* 10.—E. J. M., a 33-year-old man, complained of progressive visual deterioration for two and a half years before admission to hospital under Sir Francis Walshe. His sight was particularly impaired to the right side and he frequently walked into objects on that side. In the last two years he awakened each morning with a mild frontal headache most pronounced on the right side which lasted for one hour. It was a dull ache aggravated by coughing and stooping and relieved by aspirin. The headache only occurred at other times of the day if he had previously reclined, as in an occasional afternoon nap. Examination revealed bilateral anosmia, slight swelling of the left optic disc, and slight proptosis of the right eye. Visual acuity was 6/24 on the right and 6/36 on the left. There was an incongruous partial right homonomous hemianopia most marked in the lower quadrants and with macular sparing. There was some left facial flattening and brisker deep tendon reflexes on the left side.

*Investigations.*—Skull X-ray showed an area of decalcification in the region of the cribiform plate and an abnormal vascular marking in the floor of the left anterior fossa. The left foramen spinosum was larger than the right. The sella was slightly enlarged and the dorsum sellæ thin. The appearances suggested an olfactory groove meningioma and increased intracranial pressure. EEG revealed low voltage theta activity on the left side and a focus of moderate voltage 2 c/s waves in the mid-temporal region. At ventriculography air replacement was performed through a right posterior parietal burr-hole and only the right lateral ventricle and third ventricle filled. The septum pellucidum was displaced 1 cm. to the right of the mid-line. Probing through a left posterior parietal burr-hole encountered a firm mass at a depth of 2 cm. Left carotid arteriography revealed upward displacement of the Sylvian group of vessels and splaying of the carotid siphon. The anterior cerebral artery was displaced 1·3 cm. to the right of the mid-line. This was interpreted as a large space-occupying mass in the region of the left temporal lobe. Biopsy of this mass was later performed and histological examination revealed its nature.

*Operation.*—Exploratory tappings with the cannula detected the tumour at a depth of 1 cm. from the cortex in the region of the angular gyrus. A 3 cm. vertical incision was made in the posterior parietal cortex and the tumour exposed in the lateral ventricle. Exploration of the periphery of the mass disclosed no apparent attachment and while this procedure was in progress the tumour suddenly presented itself through the opening in the cortex. It was a lobulated and encapsulated meningioma with large vascular channels running under the capsule and leading to the choroid plexus. The specimen weighed 150 grammes and was composed of tightly interlacing bundles of ill-defined spindle-shaped cells and small islands of endothelial cells. The spindle

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cells had a tendency to stream around the numerous blood vessels permeating the tumour. A few psammoma bodies were seen.

The post-operative course was complicated by fever and a bloody cerebrospinal fluid discharge from the operative site. In the following weeks the patient's general condition had greatly improved but the dysphasia was still severe. There was some mental retardation and a right homonomous hemianopia with macular sparing. In the period after discharge from hospital there was considerable improvement in speech function which was only mildly defective sixteen months post-operatively. The patient was capable of returning to his previous employment as a labourer.

### Comment

The homonomous hemianopia proved a valid localizing sign of the tumour. However, there was the misleading feature of pyramidal signs ipsilateral to the tumour, and the notable absence of dysphasia in this case with a large tumour in the posterior part of the dominant cerebral hemisphere which distended the covering brain to a shell of 1 cm. thickness. Investigation added little to the clinical localization. The mobility of the tumour was emphasized by the extraordinary surgical delivery.

*Case* 11.—A. I., an 18-year-old Cypriot girl, was admitted under Sir Charles Symonds. Two and a half years previously her menstrual periods ceased for several months after which they were sparse and irregular. Four and a half months before admission she complained of left temporal headaches most severe upon awakening, increased by straining, and frequently associated with vomiting. For four months she was unable to feel what she was chewing in the left side of her mouth and unable to crack nuts on that side. For three months there was progressive visual deterioration in the left eye. She had experienced intermittent double vision in the past two and a half years, but not since the onset of visual failure, and had gained 14 lb. in the past two years. She had noticed fullness of the face and prominence of the eyes in the past few months. At examination the interpreter thought the patient silly and "retarded." Visual acuity was 6/6 on the right while on the left there was perception of light only. Secondary optic atrophy was present bilaterally. There was constriction of the peripheral visual field of the right eye and a temporal homonomous defect most marked in the lower quadrant. There was moderate exophthalmos, failure of full lateral horizontal deviation of the eyes, and defective convergence. The pupillary reaction was sluggish. Impairment to pin-prick and cotton-wool sensation was present in the first and second divisions of the left fifth cranial nerve. She had a round "moonlike" face. There were purple striæ over the hips. The axillary hair was sparse. Blood pressure was 140/90.

The clinical diagnosis was of an intrasellar tumour with parasellar extension.

*Investigations.*—Skull X-ray showed slight suture diastasis and prominent convolutional markings. The pituitary fossa was enlarged and excavated; the appearances suggested an intrasellar lesion. There was an area of calcification 1·5 cm. below and 1 cm. to the right of the normal pineal position. It was thought unlikely to be the calcified pineal, although a very large mid-line lesion causing depression and deviation of the pineal gland and secondary sella changes was deemed possible. EEG showed irregular slow waves in the left mid-temporal region and short bursts of regular 2–3 c/s waves in the left posterior temporal region. At ventriculography there was gross dilatation of the right lateral ventricle and of the anterior end of the third ventricle. The septum pellucidum and the third ventricle were shifted to the right of the mid-line 1 cm. anteriorly and 1·7 cm. posteriorly. Posteriorly the body

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of the left lateral ventricle was filled by a large space-occupying mass outlined by a shell of air inferiorly and medially. The anterior end of the left temporal horn was grossly dilated and multilocular (fig. 10). Small islands of air were trapped around the tumour on changes in head posture. The complete blood count, sedimentation rate, Wassermann test, and urine examination were normal. The twenty-four-hour urinary 17-ketosteroid level was 7·7 mg.

*Operation* was performed through a 3 cm. cortical incision directly over the tumour. Large quantities of the tumour were cored out. The mass had an enormous extension into the temporal horn and far forward into the body of the ventricle. It was completely removed. A arge pedicle of vessels from the choroid plexus supplied the tumour. The intact specimen weighed 158 grammes. It was a meningioma formed of bundles of elongated cells and clusters of large cells with clear round nuclei. Numerous strands of collagen permeated the tumour.

Post-operatively, the patient had severe dysphasia, complete right homonymous hemianopia, and a gross right hemiparesis. In the following weeks there was rapid improvement in speech function, lesser improvement in the right sided weakness, and no change in the hemianopia. In the following years the patient was reported as healthy with no evidence of dysphasia or endocrine abnormality and with only mild complaints referable to the visual impairment.

## Comment

The prominent false localizing signs of endocrine dysfunction and left fifth cranial nerve palsy pointed to the diagnosis of a lesion in the region of the sella turcica. Straight X-ray changes supported this diagnosis. The EEG was the first investigation which localized the tumour.

There was a history of intermittent diplopia before the onset of visual disturbance. Ventriculography revealed gross dilatation of the anterior end of the left temporal horn with trapping of islands of air around the tumour on changes of head posture.

## Discussion

### *General Features*

Meningiomas within the lateral ventricles are more frequent in the left hemisphere and, in the present study, 8 of 11 were left sided. The tumours are generally found in the trigone with local expansion and variable prolongation into the temporal horn, posterior horn, and body of the lateral ventricle; rarely they extend forward into the anterior horn and project into the third ventricle through the foramen of Monro (Case 9), and cases have been described with extension into the opposite lateral ventricle by growth through the foramena of Monro (Tschernyscheff *et al.*, 1930). Meningiomas are slightly more common in females and this differential frequency is true of lateral ventricular meningiomas. The age distribution does not significantly differ from that of other meningiomas with the maximum incidence in the third and fourth decade, although slight "shift to the left" with a higher incidence in earlier age was present in this series and has been noted in the past (Cushing and Eisenhardt,

1938; Huang, 1952). The length of history is similar to that of the group of meningiomas as a whole.

*Histology*

The presence of meningiomas entirely free of dural attachment resolved the controversy of the origin of meningiomas in favour of the arachnoid—probably from nests of arachnoid cells. Cushing and Eisenhardt (1938) emphasized the fibrous nature of these tumours and believed "true plexus meningiomas" were more highly psammomatous than the "lateral velum tumours." Abbott and Courville (1942) found two major histological types; a fibroblastic variety, and a meningothelial type with a predominance of syncitial cells. Wall (1954) showed that there was a continum rather than division with differing proportions of fibrous and syncitial cells. Huang and Araki (1954) believed that there were no microscopic differences from meningiomas located anywhere in the cranium. In the present study there were no distinctive histological features. The entire gamut of varieties were represented from fibrous, meningothelial, and combined forms, to hæmangio-endotheliomas, meningiomas with malignant features, and overtly sarcomatous meningiomas. Although the histological definition of "meningioma" is to some extent a matter of opinion there seems little inherent reason to circumscribe the categorization in these ventricular tumours. The histological pictures were sequential and largely representative of those found in meningiomas located anywhere in the cranium.

*Clinical Picture*

Cushing and Eisenhardt (1938) formulated a clinical syndrome ostensibly "fairly characteristic of lateral tumours of the velum." They utilized 2 personal cases and briefly reviewed 17 others previously reported in compiling the following characteristics: pressure symptoms with headache tending to be ipsilateral to the tumour, contralateral homonomous hemianopia often with macular splitting, contralateral sensory and motor hemiparesis more pronounced in the sensory sphere and sometimes associated with trigeminal numbness, cerebellar symptoms in more than half of the cases, and "almost invariably paralexia increased by operation when the tumour, as it commonly does, occupies the left hemisphere." Much deference has been paid to these criteria in later studies and they are regularly presented as definitive and representative of the group of lateral ventricular meningiomas.

It is noteworthy that 6 of the 11 cases in our series presented with evidence of increased intracranial pressure either without localizing signs or with dominant false localizing signs; in all 6 cases the tumour was situated in the left hemisphere. The frequent occurrence of the syndrome of isolated hydrocephalus or hydrocephalus with prominent false local-

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izing signs is confirmed by the published cases histories of lateral ventricular meningiomas reported by Tschernyscheff *et al.* (1930), Dandy (1934), Cushing and Eisenhardt (1938), Gardner and Turner, (1938), Jefferson and Jackson (1938), Knight (1949), Huber (1950), Ameli (1952), Chavany *et al.* (1952), Huang and Araki (1954), and others. In the days before widespread use of ventriculography a diagnosis of an infratentorial tumour was frequently made and posterior fossa exploration contemplated and sometimes performed. Recent reports of vertebral angiography in the investigation of cases with lateral ventricular meningiomas can only be attributed to the tentative clinical diagnosis of a posterior fossa tumour. The lateral ventricular region is one of the "silent areas" of the brain. In a review of false localizing signs in intracranial meningiomas (Gassel, 1961) the frequency of these signs was best related to the large size of the tumour. Meningiomas within the lateral ventricles were among the largest in size. False clinical localization, which results from the presence of false localizing signs and the absence or obscuration of localizing signs, was particularly common in intraventricular meningiomas.

Of the 5 cases presenting with clinical evidence of local disease, contralateral homonomous hemianopia was the sign of greatest intrinsic value in clinical localization and was present in 4 cases. The hemianopia varied in extent but was typically incomplete and most evident in the lower quadrants with slight incongruity and macular sparing. It was of the type suggestive of a lesion in the upper optic radiation. A contralateral sensorimotor hemiparesis with no particular dominance of sensory or motor defect was found in 2 cases, and isolated motor paresis in 1. Busch (1939) found contralateral motor signs decidedly more frequent than sensory signs. The putative predominance of sensory impairment in contralateral sensorimotor defect is of no value as a differential feature. Ipsilateral headache was initially reported by Dandy (1934) who indicated the limited reliability of this sign. It was rarely a prominent feature in other cases reported in the literature and was not found in any of the cases in the present series; in the 1 case in which headache was clearly lateralized, it was contralateral to the tumour. The "almost invariable paralexia in these commonly left hemisphere tumours" described by Cushing and Eisenhardt is not a conclusion easily formulated from the case histories précised by these authors. In fact, disturbance of speech function is a surprisingly infrequent finding in lateral ventricular meningiomas. In the present study there was only 1 case with mild nominal dysphasia and this occurred in a patient with some intellectual deterioration. The rarity of this finding is quite remarkable in view of the presence of huge tumours in the posterior part of the dominant hemisphere with extreme distention of the cortex, sometimes measuring as little as 1 cm. in depth. It supports the artificiality of subcortical aphasia, previously dialectically discarded by Hughlings Jackson and Freud.

With regard to other findings, papillœdema is an almost constant sign in the cases reported. Epileptic fits are infrequently described. Contrary to some reports (Gross, 1939; Wall, 1954) mental changes have no specific regional character, are not particularly severe, and are no more frequent than in intracranial meningiomas as a whole.

In the entire series of 250 meningiomas reviewed, intermittency of signs and symptoms was noted in 17 cases. All of these had either pronounced remissions in the illness or episodic headaches related to head posture and generally associated with transient appearance of signs. In retrospective analysis 6 of these cases were found in the total of 11 lateral ventricular meningiomas, a marked preponderance.

There has been a medley of reports of intermittent exacerbations in the history of illness of patients with intracranial masses. Bruns (1902) originally reported acute attacks of violent headache, neck stiffness, vomiting, and severe vertigo precipitated by the changes in head position in a patient with cysticercosis infestation of the fourth ventricle. There was freedom from complaints in between attacks and the patient was able to avoid them by refraining from sudden movements of his head. This symptom complex was reaffirmed in fourth ventricular cysticercosis (Henneberg, 1906; Stern, 1907) and later found in a variety of tumours in the region of the fourth ventricle (Marburg, 1926; van Bogaert and Martin, 1928). It was entitled *Bruns symptom* (Oppenheim, 1911). Fixation of the head in flexion, extension, or rotation during the attacks was reported (Henneberg, 1906; Stern, 1907; Stenvers, 1925). Head posturing was found between attacks (Henneberg, 1906; Stern, 1907; Marburg, 1926; van Bogaert and Martin, 1928), and later emphasized as part of *Bruns syndrome* (Alpers and Yaskin, 1944). Alpers and Yaskin included in this syndrome cases of cerebellar tumours, third ventricular cysts (Weisenburg, 1910; Dandy, 1933), lateral ventricular masses (Dandy, 1934), and a case presumptively diagnosed as disseminated sclerosis, with a wide variety of symptoms produced on changes in head posture. Some of these patients had isolated complaints such as occasional slight dizziness more on bending forward, or dizziness and obscuration of vision on suddenly sitting up in bed or quickly changing position in the erect posture. Such symptoms in patients with intracranial tumour and increased intracranial pressure are much too non-specific to categorize. Some of the other cases incorporated in Bruns syndrome, including many of the patients with cerebellar neoplasm, had pronounced posturally influenced vertigo without associated headache or neck stiffness. Isolated postural vertigo seems sufficiently distinct from Bruns' original description to warrant classification as a separate type of central positional vertigo. Alpers and Yaskin also emphasized the absence of posturing of the head in Bruns syndrome caused by tumours in the third or lateral ventricles in differentiation from Bruns syndrome caused by posterior fossa lesions in which head postur-

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ing is frequently present. Head posturing occurred in Case 2 of the present series and was a pronounced feature in cases of lateral ventricular meningioma described by Gardner and Turner (1938), Busch (1939), and Knight (1949).

Bruns syndrome aside, cases with intermittent symptoms frequently occurring at the height of the headache, pronounced postural incidence of the headache, or remissions in the course of the illness were decidedly more common in meningiomas in the lateral ventricle in this study. Many of the reported case histories of lateral ventricular meningiomas describe such features (Christophe *et al.*, 1934; Fincher, 1934; Love, 1935; Cushing and Eisenhardt, 1938; Gardner and Turner, 1938; Jefferson and Jackson, 1938; Busch, 1939; Campbell and Whitfield, 1940; Knight, 1949; and Wall, 1954). Weisenburg (1910) suggested intermittent obstruction to the outflow of C.S.F. by a mobile intraventricular mass in explanation of episodic signs in a case of third ventricular cyst. Dandy (1934) believed that a similar mechanism functioned with mobile tumours in the lateral ventricles with the production of a ball and valve dynamic; he noted a particular enlargement of the ipsilateral temporal horn in support of this concept. The rapidity of these changes on alteration in head posture caused him additionally to postulate some sort of vascular obstruction and hyperæmia local to the tumour. Cases 1, 2, 3, 4, 5, 6 and 11 demonstrated an intermittent block in cerebrospinal fluid circulation with incarceration of air within the blocked temporal or anterior horn on ventriculography. Case 1 illustrated a remarkable decrease in deviation of the septum pellucidum after evacuation of the obstructed and encysted anterior horn. The anterior horn filled with air in subsequent injection. "Endothelial cysts" under high pressure have frequently been described at operation on lateral ventricular meningiomas (Christophe *et al.*, 1934; Cushing and Eisenhardt, 1938; Gardner and Turner, 1938; Knight, 1949; Huang and Araki, 1954; and Wall, 1954); and a rapid decompression and sometimes remarkable clinical improvement has followed evacuation of the "cyst." The intermittent block with peripheral distension of the occluded ventricular horn might account for such local symptoms as the hemianopic aura to the headache in Case 2 or the intermittent contralateral hemiparesis in Case 3. It would also result in sudden increase in the effective size of the tumour and transient displacement of the brain. Many of the signs appearing during intermittent exacerbations, generally at the height of the headache, can be attributed to reversible mechanical distortions and displacements of the brain with varying degrees of herniation through the dural compartments. Cranial nerve palsies (Collier, 1904), pyramidal signs (Kernohan and Woltman, 1929), ataxia (Grant, 1928), posterior column signs (Batten and Collier, 1899), neck stiffness and altered attitude of the head (Vincent, 1936), positional nystagmus and vertigo (Nylén, 1931), autonomic

changes (Vincent, 1936), anisocoria (Sunderland and Bradley, 1953), atypical "fits" without convulsions sometimes lasting for hours to days (Schwarz and Rosner, 1941), and decerebrate rigidity (Jefferson, 1938) have previously been related to the effects of displacements of the brain at a distance to the primary space-occupying mass and have all been described in these episodes. The transient facial paræsthesiæ (Cases 2, 3, and 4) may be understood on a similar basis with intermittent distant effect on the extramedullary fifth cranial nerve, later represented in the palsy of this nerve as a false localizing sign in other cases (Cases 2 and 11). Other of these transient signs have been observed as permanent false localizing signs when periodic functional impairment is translated into structural change by severe and prolonged pressure effect.

Intermittency of signs was also found in 11 of 239 meningiomas in this study which were situated in diverse locations of the brain other than intraventricular in position. It has been reported as an infrequent finding in a wide variety of tumours within the cranium (Collier, 1904; Schwarz and Rosner, 1941; and Kelly, 1951). The sudden onset of many of the episodes suggests a vascular factor in production. Dandy (1937) and Ecker (1955) have observed sudden transient elevations in cerebrospinal fluid pressure, independent of the pulse rate and blood pressure, in quiet or sedated patients with increased intracranial pressure. These changes can only be attributed to temporary increases in the intracranial blood volume incident to tonic changes in cerebrovascular tone (Ryder *et al.*, 1951; Ecker, 1955). Such dynamic change in a tumour with borderline hydrodynamic adjustment might result in distension of an already herniated temporal lobe or initiate such a herniation, and cause mid-brain distortion or vascular insufficiency which is reversible. Some of the more prolonged phenomena may result from transient cerebral œdema. Œdema in the neighbourhood of a tumour has been emphasized as the precipitating mechanism of acute symptoms by many authors (Collier, 1904; Scheinker, 1945). That œdema may be catastrophic in onset is an established surgical observation. Sudden reversible vascular change leading to transient increase in the size of the intracranial mass, either by temporary increase in intracranial blood volume or evanescent cerebral œdema, and resulting in reversible displacement of the brain may account for some of these episodes.

## Investigations

*Radiology.—Straight skull X-rays* revealed changes of elevated intracranial pressure in 8 of 11 cases. In two cases the sella turcica destruction was pronounced and a primary intrapituitary neoplasm was diagnosed. Diffuse calcification of the mass occurred in one case but the calcification was neither diagnostic of the intraventricular position nor suggestive of the histology of the tumour. Pineal shift lateralized the mass in two

cases and in one other this displacement was so marked that the calcification was thought unlikely to be pineal in origin.

*Carotid arteriography* was performed in 2 cases and revealed displacement of vessels indicative of a deeply situated local mass, but, as in most previous studies, the intraventricular position was not diagnosed; however, it has been reported that an enlarged anterior choroidal artery ending in a tuft of vessels (Huang and Araki, 1954; Wall, 1954) or a local accumulation of contrast in the phlebogram may suggest the diagnosis (Huang and Araki, 1954).

*Vertebral angiography* may show disturbances of the choroid plexus pattern or outline the tumour by encircling vessels (Ameli, 1953; Wall, 1954).

At *ventriculography* a higher protein level is occasionally found in the ventricular fluid sample from the side of the tumour. Operative needling sometimes encounters a firm sub-cortical mass which may be movable; and "cysts" under high pressure, representing occluded ventricular horns, may be punctured. In the present series ventriculography was performed in all cases and demonstrated an intraventricular mass by encircling it with a shell of air in 6 of 11 cases. In 3 cases a mass distorting or obstructing the ventricular system was diagnosed but not the specific intraventricular position. Trapping of air in the ventricular horns on changes of head posture is diagnostic of a mobile intraventricular tumour and would have localized the tumour in 2 of these 3 cases. In the remaining 2 cases there was non-filling of the affected side with displacement of the septum pellucidum lateralizing the tumour. Non-filling of the ipsilateral ventricle was reported in 2 of 3 cases by Huber (1950) and in 3 of 6 cases by Huang (1952), Huang and Araki (1954). Huber noted that the deviation of the septum pellucidum was most pronounced posteriorly, localizing the tumour to the posterior hemisphere. This differential displacement of the septum pellucidum was present in most but not all cases in the present series.

*Electroencephalography*.—Electroencephalography was performed in 10 of 11 cases. There were slow waves which localized the tumour in all instances. The abnormalities were sometimes rhythmic and episodic and suggested a deep hemisphere lesion in three instances. The only case with pre-operative epilepsy had clearly defined mid-temporal spikes. Electroencephalography localized the tumour in the 4 additional cases reported in the literature. This efficacy is in contrast to reports of the EEG in subcortical or intraventricular tumours other than meningiomas in which local abnormalities are infrequent. Cobb and Gassel (1960) suggested that the difference may be accounted for by the larger size of intraventricular meningiomas before they present with clinical evidence of disturbed function.

*Operative removal.*—When the diagnosis of a lateral ventricular tumour is established pre-operatively the chance of removal and cure is excellent. The usual approach is by incision directly over the tumour which generally separates with ease and is readily delivered either piecemeal or *in toto*. Wall (1954) suggests making the incision as far posteriorly and inferiorly as possible, in the usual trigonal tumour, to avoid post-operative sensory and symbolic defect. Cramer (1960) advises a posterior linear incision in the occipitoparietal cortex with extraction of the tumour *in toto* and hæmostasis of the aftercoming choroid plexus stalk, in order to minimize the operative trauma.

Post-operatively there is generally an incomplete homonomous hemianopia, some contralateral sensorimotor paresis, and dysphasia—when the tumour affects the dominant hemisphere. There is usually rapid improvement in the motor disability, satisfactory return of sensibility, considerable return of speech function, and no change in the homonomous hemianopia; and it is surprising how limited is the long term practical disability incurred by surgery in most patients.

## Summary and Conclusions

Meningiomas within the lateral ventricles are fundamentally extracerebral tumours. They arise in the region of the trigone, more frequently in the left hemisphere, and their growth tends to conform to the cast of the ventricle; sometimes they extend through the foramen of Monro into the third ventricle. They are mobile neoplasms at some period of their development and compress rather than invade the brain. These tumours present particular diagnostic difficulties which are related to their anatomical characteristics. They generally grow to a large size before symptoms of illness appear. Patients frequently present clinically with isolated hydrocephalus or with dominant false localizing signs. Local signs, when present, do not differentiate lateral ventricular meningiomas from the group of posterior hemisphere tumours. However, posturally influenced headache and other episodic signs are common in, although not particular to, lateral ventricular meningiomas. The periodicity has been related to intermittent obstruction and distension of a ventricular horn by the mobile tumour causing increase in the effective local mass and transient displacement of the brain.

Investigations may be diagnostic of the intraventricular position of the tumour but frequently reveal evidence only of a deep posterior cerebral hemisphere mass. Straight X-rays contribute little specific information. Carotid arteriograms may show some abnormality of the choroidal circulation or rarely a typical meningioma "blush," but generally reveal only vessel displacement consistent with a deep space-occupying mass. Electroencephalography shows local and occasionally rhythmic abnormalities which may be suggestive of a deep seated lesion. Ventriculography

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is the most reliable investigation. At ventriculography operative needling may encounter a deep, firm, and sometimes movable mass; "endothelial cysts" (which represent occluded ventricular horns) may be punctured; and a higher protein level may be found in the C.S.F. sample from the affected lateral ventricle. Air studies, sometimes diagnostic of an intraventricular mass by depicting it encircled by a shell of air or by postural trapping of air in a ventricular horn, not infrequently reveal either non-filling of the affected side with deviation of the ventricular system or a non-specific ventricular obstructing mass.

Diagnosis is especially important because of the excellent prognosis of surgical removal. However, certain features may militate against radical investigative procedures and surgical intervention. The location deep in the posterior part of the cerebral hemisphere is an unusual situation for benign neoplasms. Investigations, when not diagnostic, are generally interpreted as most likely to be a glioma. The usual location in the dominant hemisphere in proximity to the vulnerable speech centres magnifies the calculated risk of operation.

Some of the findings, insignificant in isolation, contribute to the diagnosis of a lateral ventricular meningioma when evaluated in the overall picture. Intermittent or posturally influenced symptoms deserve particular emphasis and when associated with evidence of a deep posterior cerebral hemisphere mass are presumptive of the diagnosis. Other factors of importance are the late appearance of clinical signs of local disease and the high frequency of false localizing signs; the presence of local EEG abnormalities; and operative puncture of "cysts," exploratory needling of a deep firm and sometimes movable mass, and discrepancies in the cerebrospinal fluid protein levels from the lateral ventricles.

We wish to thank the Medical Committee of the National Hospital for permission to publish this report and the physicians and surgeons for the use of the case records of their patients.

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FIG. 1A.—Dilated left trigone and occipital horn.

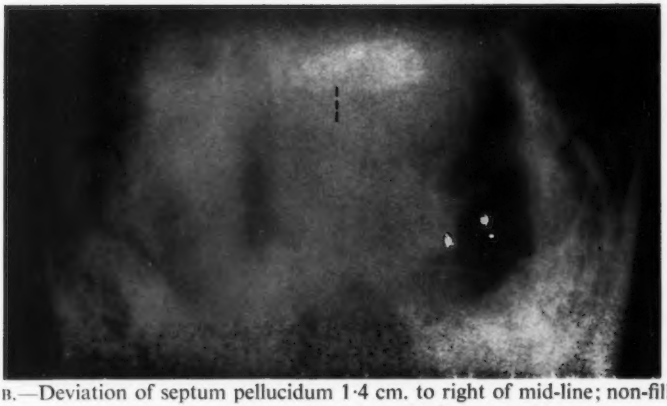

FIG. 1B.—Deviation of septum pellucidum 1·4 cm. to right of mid-line; non-filling of left anterior horn; gross dilatation of left temporal horn.

*To illustrate article by M. M. Gassel and Hugh Davies.*

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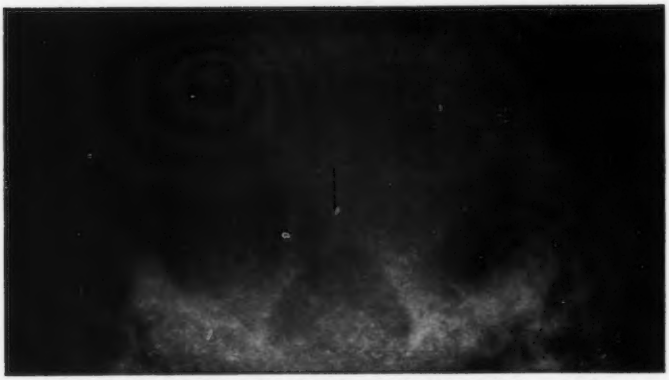

FIG. 1C.—Diminished displacement of septum pellucidum (0·9 cm.) after tapping of "cyst"; left anterior horn now filled with air.

FIG. 1D.—Air trapped anterior to tumour (brow-down).

*To illustrate article by M. M. Gassel and Hugh Davies.*

FIG. 2.—Air trapped in grossly dilated right temporal horn (brow-down).

FIG. 3A.—Air outlining tumour; right temporal horn widely dilated (brow-up).

*To illustrate article by M. M. Gassel and Hugh Davies.*

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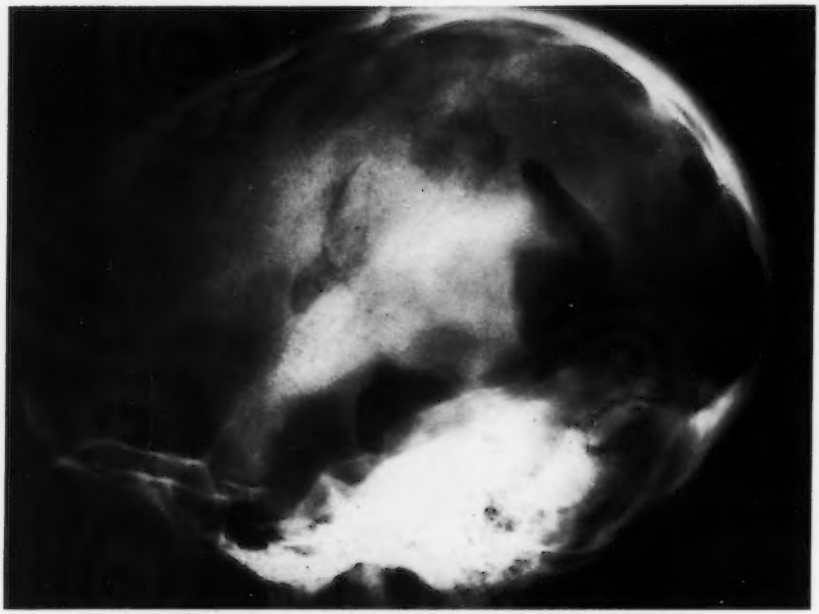

FIG. 3B.—Obstruction to emptying of right temporal horn (brow-down).

FIG. 4.—Air trapped anterior to tumour (brow-down).

*To illustrate article by M. M. Gassel and Hugh Davies.*

FIG. 5A.—Dilated left temporal horn; moderate degree of shift of septum pellucidum to right anteriorly (brow-up).

FIG. 5B.—Marked shift of septum pellucidum to right posteriorly and compression of third ventricle (brow-down).

*To illustrate article by M. M. Gassel and Hugh Davies.*

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FIG. 6A.—Air trapped anterior to tumour in left lateral ventricle (brow-down).

FIG. 6B.—Filling defect in posterior part of left lateral ventricle; air partly outlining tumour (brow-down).

*To illustrate article by M. M. Gassel and Hugh Davies.*

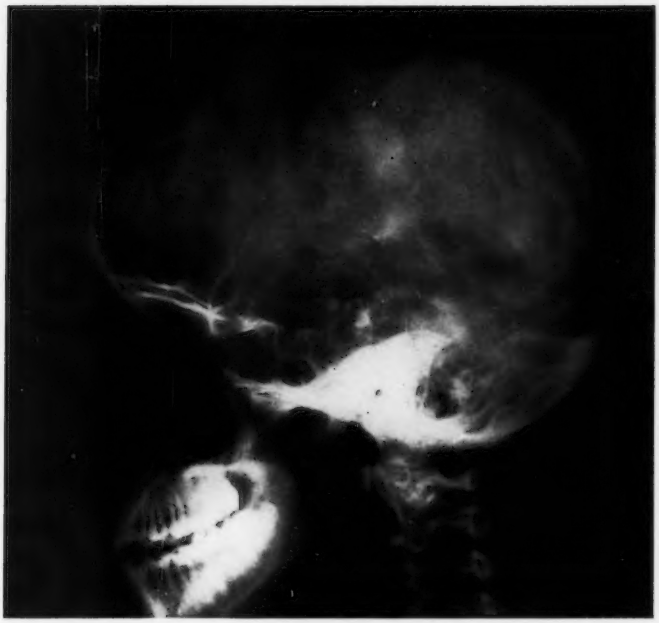

FIG. 7A.—Left temporal calcification.

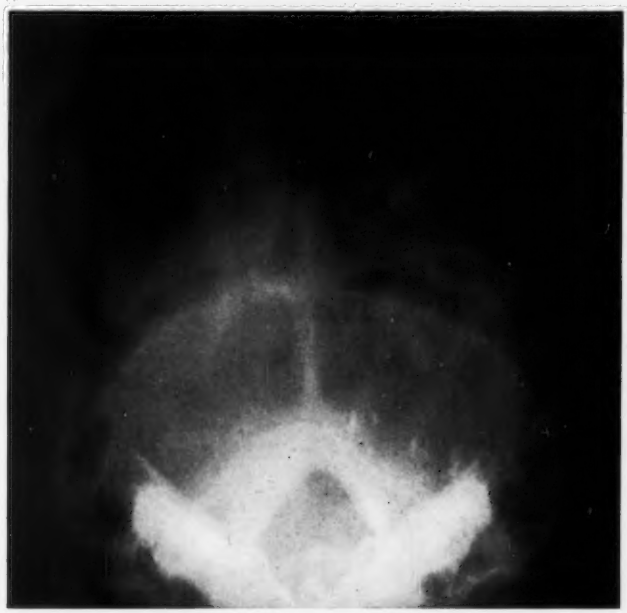

FIG. 7B.—Left temporal calcification.

*To illustrate article by M. M. Gassel and Hugh Davies.*

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FIG. 8A.—Air outlining tumour in left trigone (brow-down).

FIG. 8B.—Air outlining tumour in left trigone (brow-down).

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FIG. 9.—Mass outlined by air in left lateral ventricle (brow-down).

FIG. 10.—Mass in the left trigone outlined medially and inferiorly by air (brow-down).

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# THE DIAGNOSIS OF THE CHOROID PLEXUS PAPILLOMA OF THE LATERAL VENTRICLE

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## INTRODUCTION

CHOROID plexus tumours are rare in general neurosurgical practice, where they make up only about 0·5 per cent of all the intracranial tumours seen, as in the series of Cushing (1932), Grant (1956), Zülch (1950) and Olivecrona (Hoessly and Olivecrona, 1955). In pædiatric clinics on the other hand, they account for up to 3 per cent of brain tumours encountered (Ingraham and Matson, 1954; Odom *et al.*, 1956; Bodian and Lawson, 1953), though in one series, that of Cuneo and Rand (1952), they amounted to 1 in 28 of the cases. These tumours are not usually malignant and few seed within the ventricular system or the subarachnoid space. The cases assume considerable importance in children, as they constitute one of the types of intracranial tumour which, theoretically at least, are operable with hope of permanent success.

These tumours present great diagnostic problems, especially when they are situated within the lateral ventricle, where there may be no localizing signs, and progressive hydrocephalus is often the only feature. This difficulty is underlined by the large proportion of unexpected post-mortem findings amongst the 400 or so cases reported in the literature. Some cases have been discovered on air encephalography, such as those of Zander (1949), Bertha and Sorgo (1940) and Kahn and Luros (1952), or after angiography such as those of Abbott *et al.* (1957) and Ernsting (1955), or even by the discovery of tumour cells in the cerebrospinal fluid such as that of Musaelian (1940). In other instances, the condition was not recognized until the tumour was visualized upon the operating table, as in the cases of Dandy (1934), Jefferson and Jackson (1939), Matson (1953) and Ray and Peck (1956) amongst others. Only a few cases have been operated upon with permanent success, exemplified by the classical

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case of Perthes (1919), those of Kahn and Luros (1952), Ingraham and Matson (1954) and Carrea *et al.* (1955). It is hoped that the following cases may underline some clinical features, and help in speedier and more accurate diagnosis of the lateral ventricular choroid plexus papillomata, which make up the bulk of the plexus tumours in childhood.

## Case Reports

*Case* 1.—H. W. had an uneventful infancy following normal pregnancy and delivery. At 15 months, after being able to walk and stand unaided she developed, what was thought, in retrospect, to have been whooping cough. She then became progressively ataxic and latterly was unable to stand unsupported. She was then noted to have an enlarged head.

When admitted at the age of 2 years, she was a happy but markedly ataxic child with head circumference of $20\frac{3}{8}$ in. (normal average 19 in.). Early papillœdema and exaggerated reflexes with increased limb tone and equivocal Babinski response were found.

At ventriculography, cerebrospinal fluid containing 90 mg. per cent of protein, and 4 leucocytes per c.mm. under considerably increased pressure was encountered at a depth of 2 cm. The bubble air ventriculogram showed a grossly but symmetrically dilated ventricular system, with a fourth ventricle so dilated that it had assimilated most of the aqueduct. The air which passed into a hugely dilated cisterna magna did not pass above the level of the interpeduncular system. Films taken two hours later failed to demonstrate any air above the level of the tentorium.

Two days after ventriculography the child became progressively drowsy and irritable, and the papillœdema increased. Removal of 40 c.c. of cerebrospinal fluid by ventricular puncture produced a noticeable but only transient improvement. During the following two weeks in spite of daily lumbar punctures at which between 20 and 40 c.c. of cerebrospinal fluid were released, her condition continued to deteriorate slightly, with the development of bilateral external rectus palsy.

During the last week of her life her condition deteriorated rapidly, with progressive drowsiness, irritability and a ventricular pressure of more than 300 mm. of water. Terminally she developed decerebrate rigidity and had almost incessant convulsions in spite of continuous ventricular drainage, and she died twenty-three days after the original ventricular puncture.

At autopsy, apart from congestion of the lower lobes of the lungs, a stomach containing a moderate amount of altered blood and a duodenum with a terminal perforating ulcer 5 mm. in diameter, all other positive findings were within the skull or within the central nervous system.

The brain, which weighed 1,042 grammes after the C.S.F. had been drained, showed considerable convolutional flattening and some arachnoidal thickening. The ventricular system was severely but symmetrically dilated, the lateral ventricles measuring about 7 cm. in diameter. A rounded friable congested cauliflower tumour measuring $4{\cdot}5 \times 3{\cdot}2 \times 3$ cm. was situated in the trigone of the left lateral ventricle, and was attached to the glomus of the choroid plexus anteriorly, and to the lateral ventricular wall by a glial strand posteriorly (fig. 1, Plate LXXVI). The remainder of that plexus and the other choroid plexuses appeared normal. The cerebral mantle was greatly thinned, with grey matter of normal dimensions and appearance but a grossly reduced and congested white matter. Numerous subependymal petechial hæmorrhages were present, particularly in the left lateral ventricle and the corpus callosum which also contained a number of larger hæmorrhages. Granular ependymitis was marked and widespread. The third and fourth ventricles and the aqueduct were also severely

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dilated, while the cerebellum was flattened by a large cisterna magna (fig. 2). The interpeduncular cistern was also dilated. The spinal cord was normal though covered with moderately thickened arachnoid.

Microscopy of the tumour showed the typical appearance of a choroid plexus papilloma with grossly congested blood vessels.

*Case* 2.—C. P., after a normal pregnancy and delivery, developed normally for the first year. She then failed to progress, became increasingly sleepy and disinterested in her surroundings and meals. Slight left internal strabismus, and occasional right-sided facial twitching but no head enlargement were observed.

When she was admitted at 15 months of age, the head circumference was 20½ in. (normal average 18¼ in.), and she was considered backward. The anterior fontanelle was small but tense. Early papillœdema, slight neck rigidity and weakness of the right arm and leg were noticed.

At ventriculography clear, colourless cerebrospinal fluid under greatly raised tension, and containing 60 mg. of protein and 15 red blood cells per c.mm. was encountered at a depth of 2 cm. The radiographs showed a severely but symmetrically dilated ventricular system and basal cisterns. Air was thought at the time to have passed through the tentorium into the sylvian fissures. On later review of the X-ray films this appearance was found to be due to air trapped by the tumour in the presence of a basal cistern block.

During the twenty-four hours following ventriculography, the fontanelle tension and papillœdema increased and the child became progressively drowsy, so that ventricular drainage had to be instituted. Although about 250 c.c. of cerebrospinal fluid was drained daily she deteriorated further and died on the fifth day following the first ventricular puncture.

At autopsy, apart from early bronchopneumonic changes all the significant findings were in the central nervous system. The brain which weighed 1,240 grammes after the cerebrospinal fluid had been allowed to drain, showed a little convolutional flattening, moderate thickening and opacity of the arachnoid and a subarachnoid space of unusual width for a case of hydrocephalus. The whole ventricular system was severely and symmetrically dilated, the lateral ventricles measuring about 4 cm. in diameter. A highly congested friable, cauliflower-like rounded tumour measuring approximately 6·5×4×4 cm. was situated in the inferior and posterior horns of the right lateral ventricle and was attached to the posterior end of the choroid plexus, and to the thalamus by a few delicate glial strands (fig. 3). Some recent blood clot covered part of the tumour. The ependymal lining throughout was moderately thickened and showed marked granular ependymitis, while in the vicinity of the tumour it showed considerable hæmosiderin staining in addition. The remainder of the plexus in the right lateral ventricle and other choroid plexuses appeared normal. The cerebral mantle was considerably reduced in extent and measured approximately 2 cm. in thickness. The cerebellum was indented inferiorly by a very large cisterna magna and the other basal cisterns also appeared considerably dilated. Spinal cord was normal but covered by thickened meninges.

Microscopically this tumour was a highly congested typical choroid plexus papilloma. This case has been briefly reported elsewhere (Laurence, 1958).

*Case* 3.—I. C. developed normally after a normal pregnancy and delivery, until the age of 7 months, when he was thought to have had rubella. He made a partial recovery, but then became irritable and began to vomit his feeds. At 8 months he was noticed to be backward and hydrocephalic. There was bilateral papillœdema. A lumbar puncture yielded clear cerebrospinal fluid with a raised protein content, under considerably raised tension.

He was admitted to The Hospital for Sick Children at 8½ months of age with a head circumference of 19¾ in. (normal average 17½ in.). In addition to the previous findings, a left internal strabismus, some facial weakness and general hypotonia were found. At ventriculography, clear, colourless cerebrospinal fluid under considerably raised tension, containing 600 mg. per cent of protein, and 28 white blood cells was withdrawn. Severe dilatation of the whole ventricular system and the basal cisterns was demonstrated on the air pictures. No air passed the tentorium and it was concluded that this was a case of basal cistern block.

Immediately following the ventriculography he began to vomit and became progressively drowsy. The cerebrospinal fluid pressures remained grossly raised (300 mm. or more of water), in spite of intermittent ventricular punctures. His condition remained static until six days prior to his death, when he became unrousable, developed bladder distension and intermittent respiratory failure. Terminally he had opisthotonos and extensor spasms and died fourteen days after the ventriculography.

At post-mortem examination severe bronchopneumonia with abscess formation, fibrinous pleurisy, acute ante-mortem thrombus in the right atrium and fatty change in the liver were present.

The brain which weighed 960 grammes after the cerebrospinal fluid had been allowed to drain, was rather soft, particularly in the regions where the repeated ventricular punctures had been performed, and showed considerable convolutional flattening. The arachnoid was moderately thickened and opaque and showed some hæmosiderin staining especially in the parietal regions. The whole ventricular system was severely and symmetrically dilated with the lateral ventricles measuring approximately 4·5 cm. in diameter. A rounded plum-coloured rather mobile cauliflower-like friable tumour measuring 3½ × 4 cm. was attached to the glomus of the choroid plexus of the right lateral ventricle (fig. 4A and B). Microscopically it had the typical papillary structure, closely resembling that of the normal choroid plexus (fig. 5). The remainder of the right lateral ventricular and other choroid plexuses appeared normal. Granular ependymitis was present throughout, and the right lateral ventricle contained a number of moderate-sized recent blood clots. The cerebral tissue was reduced to approximately 2 cm. with normal grey matter and a grossly thinned white matter. The latter was soft and contained dilated blood vessels. Numerous subependymal hæmorrhages and a number of larger hæmorrhages into the corpus callosum were present.

The cerebellum was indented by a very large cisterna magna (fig. 6). A dilated chiasmatic and interpeduncular cistern elevated the floor of the third ventricle, and directly elongated the pituitary stalk and flattened the pituitary gland into the pituitary fossa. The spinal cord was normal but was covered with thickened opaque meninges. On review of the ventriculograms, the posterior surface was shown just breaking the air-fluid level in one of the films (fig. 7).

When within a comparatively short time the third case of choroid plexus papilloma was found unexpectedly at post-mortem examination in patients who were diagnosed as cases of communicating hydrocephalus, there was great concern. These cases were therefore very carefully reviewed, to see what features they had in common which might point to the correct diagnosis, so that such tumours would not be missed in the future (Table I).

Clinically all 3 developed normally for at least a year and then deteriorated quite rapidly after some ill-defined but undisputed illness. They were all found to have hydrocephalus associated with papillœdema. This latter

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TABLE I

| Case No. | Onset | Papillœdema | C.S.F. Pressure | C.S.F. Protein | C.S.F. Cells | Effect of ventriculography |
|---|---|---|---|---|---|---|
| 1 | 15/12 | + | + | 90 mg.% | 52 W.B.C.<br>24 R.B.C. | Progressive loss of consciousness four days later |
| 2 | 12/12 | + | ++ | 60 mg.% | 15 R.B.C. | Immediate progressive deterioration, with greatly raised ventricular C.S.F. pressure |
| 3 | 7/12 | + | ++ | 600 mg.% | 28 W.B.C. | Immediate progressive deterioration, with greatly raised ventricular C.S.F. pressure |
| 4 | 9/12 | ++ | ++ | 65 mg.% | 10 W.B.C.<br>640 R.B.C. | Increasing drowsiness and vomiting |
| 5 | 2½ yrs. | + | ++ | 100 mg.% | 200 R.B.C. | Immediate severe deterioration, with greatly raised ventricular C.S.F. pressure |

is a feature quite unusual in so-called idiopathic hydrocephalus in childhood and should perhaps have aroused suspicion of the presence of an intracranial tumour, which it often accompanies.

Lumbar or ventricular puncture yielded cerebrospinal fluid, always under considerably raised tension, which was xanthochromic in 2 cases and in all 3 had a raised protein or cell content. A bubble ventriculogram in each case demonstrated a considerable symmetrical hydrocephalus due to a basal cistern block. In one case air was thought to have found its way into the sylvian fissure, but in none was a tumour reported. Following air studies all 3 patients deteriorated most dramatically, with acutely raised intracranial tension and progressive drowsiness which persisted in spite of intermittent or continuous C.S.F. drainage.

It was therefore resolved that, in cases of communicating hydrocephalus associated with papillœdema, especially where the C.S.F. protein or cell content is raised, and more particularly where there should be a sudden deterioration after ventriculography, a further and more extensive air study should be carried out. More C.S.F. would be replaced in order to visualize the whole choroid plexus to determine whether a tumour is present.

Not long after, 2 such cases were seen which amply confirmed the value of the review of the previous 3 cases.

*Case* 4.—M. S. was a 10 months' old child with a normal birth and family history, who was perfectly well until three weeks before admission to The Hospital for Sick

Children, when he developed a "cold" associated with listlessness. This was followed some days later by vomiting and apparent difficulty in focusing on objects. On admission he was drowsy, febrile and resented examination. Neck rigidity was moderate, the skull circumference was $18\frac{3}{4}$ in. (normal $18\frac{1}{4}$ in.), fontanelle tension high with evident cerebral irritation. He had a left external rectus palsy, dilated pupils which reacted sluggishly to light and he had severe bilateral papillœdema. There was a general hypotonia in all limbs and the plantar response was extensor on both sides.

At lumbar puncture a moderate amount of clear cerebrospinal fluid, containing 35 mg. per cent of protein, under very greatly increased pressure was withdrawn. Following this his condition improved a little.

At ventriculography the cerebrospinal fluid now containing 65 mg. per cent of protein, 10 white blood cells and 640 red blood cells was found at a depth of 2 cm. again under considerably increased pressure. The ventriculogram demonstrated severely dilated lateral ventricles with a normal aqueduct and fourth ventricle. There was free escape of air into a large cisterna magna and thence into a dilated chiasmatic cistern. It was concluded that this was a case of hydrocephalus due to a basal cistern block.

During the next three days the child was severely ill with increasing neck stiffness, drowsiness and vomiting, which raised the possibility that there may be a choroid plexus papilloma present. A second ventriculogram was performed, this time after removing sufficient air to explore the lateral ventricles fully. A large filling defect of the body and anterior part of the trigone of the right lateral ventricle, measuring 4 cm. in its greatest diameter and having the appearance of a choroid plexus tumour, was now demonstrated (fig. 8). Immediately following this examination the child became very acutely ill with severe neck retraction, a very high fontanelle tension and laryngeal spasm.

At operation the next day the tumour was found consisting of soft pale friable fronds not unlike grossly enlarged normal plexus. Anteriorly it was covered with a thin layer of old clotted blood and the slightest touch led to severe bleeding. The tumour was removed with a pituitary rongeur and by suction. Considerable bleeding from three small arteries in the stalk was finally arrested, and when the ventricle was washed out it was possible to see that either a tumour extension or a normal choroid plexus extended posteriorly into the temporal horn. This, which proved to be choroid plexus, was elevated and removed. . Histologically the tumour was found to be a typical, well differentiated choroid plexus papilloma.

Following the operation the child had a left hemiparesis and remained apathetic. He became pyrexial and his condition began to deteriorate with limbs held in a position of extension and no response to visual stimulæ. Fontanelle tension remained high and ventricular fluid which was tapped, was faintly xanthochromic. Diarrhœa occurred and there was a persistent electrolyte imbalance with potassium depletion which was finally corrected with intravenous therapy. Terminally the child had long periods of apnœa unassociated with cyanosis and he finally died five weeks after the operation.

At post-mortem the only significant findings were within the cranium, apart from gas distension of the large intestine and some flabbiness of the heart. The brain which weighed approximately 830 grammes (without C.S.F.) was covered with normal leptomeninges over the cerebral hemispheres but beneath the tentorium where there was coning, meningeal thickening and the basal cisterns and the spinal theca were filled with a purulent exudate and old blood. The degree of internal hydrocephalus was gross with the cerebral mantle being reduced to between 1·0 and 1·5 cm. The whole of the ventricular system was filled with purulent cerebrospinal fluid. The

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choroid plexus in the left lateral ventricle appeared normal beneath a covering of pus. In the right lateral ventricle the site of the excision of the choroid plexus papilloma was easily identified and there appeared to be no residual tumour.

*Case* 5.—P. G. was a 2½-year-old boy, who though somewhat backward, was well until four weeks before admission, when he had a severe bilious attack associated with drowsiness. From this he recovered spontaneously in twenty-four hours but he had a second more prolonged episode three weeks later lasting some seventy-two hours which led to his admission, first to a general hospital and then to The Hospital for Sick Children. On admission he was drowsy but rousable, had a head circumference of 21 in. (normal average 19¾ in.) early papillœdema, large pupils which reacted sluggishly to light, some neck stiffness and brisk tendon reflexes and plantar extensor reponses.

A lumbar puncture yielded blood-stained as well as xanthochromic cerebrospinal fluid containing 100 mg. per cent of protein. An X-ray of the skull showed the ventricle was entered at a depth of 3 cm. and 60 c.c. of C.S.F. under greatly raised tension were replaced by 45 c.c. of air. Bubble air ventriculogram demonstrated severe dilatation of the lateral ventricles, the right more severe than the left, together with dilatation of the remainder of the ventricular system. Air escaped freely into the dilated basal cisterns, as far as the interpeduncular cistern, though some air was thought to have passed into the left sylvian fissure. This case was regarded as one of communicating hydrocephalus, though choroid plexus papilloma was not ruled out in view of the limitations of the air bubble technique.

Intermittent ventricular drainage had to be carried out during the next ten days as the child's condition deteriorated acutely. Further ventriculography was then performed. This time considerably more of the cerebrospinal fluid was replaced by air, in order to search for a suspected choroid plexus papilloma and a lobulated intraventricular tumour was in fact outlined in the left temporal horn (figs. 9 and 10). The air which was thought, in the previous ventriculogram, to be in the left sylvian fissure, was almost certainly air trapped by this intraventricular tumour.

At operation two days later a large pink granular tumour which filled the whole of the enlarged temporal horn of the left ventricle was removed piecemeal. Some hæmorrhage occurred from the extremely vascular stalk.

Microscopy of the tumour showed the typical structure of a benign choroid plexus papilloma.

After slight cerebrospinal fluid leakage and post-operative vomiting and dehydration which led to some electrolyte disturbance, the boy was well enough to be discharged for convalescence two weeks after the operation. His neurological state then was very greatly improved. Although the bone flap became elevated and the skull circumference increased by 2 in. during the following five months, his general condition continued to improve. During the last six months the skull ceased to enlarge, his mental and physical improvement continued and the inco-ordination, and right-sided weakness which was present largely disappeared.

Once the presence of a choroid plexus papilloma is suspected on clinical grounds, then the diagnosis rests almost entirely upon the radiological visualization of the tumour. Some features to look for and some special points of the techniques employed may be helpful:

*Radiological Diagnosis and Technique*

Skull radiographs show the usual features of hydrocephalus, namely a thin vault, large in proportion to the base and facial structures. In

addition there may be some separation of the sutures, a feature not commonly noted in hydrocephalus after the first few months of life. Tumour calcification has not been shown in these cases but has been reported (Wilkins *et al.*, 1948).

It is the practice at the Hospital for Sick Children, Great Ormond Street, to investigate hydrocephalic infants by fontanelle ventriculography followed, if necessary, by lumbar encephalography. "Bubble ventriculography" is used in which only a small volume of ventricular cerebrospinal fluid (20–40 ml.) is replaced by air in the belief that such a small volume is less likely to provoke complications than a more complete replacement. This small volume is quite sufficient to show the thickness of the cerebral mantle and by manipulation of the head it is possible to transfer the air successively into the third ventricle, aqueduct and fourth ventricle and to demonstrate any obstruction or deformity of the cerebrospinal fluid pathway within the brain. If no obstruction is found, the air will pass freely into the cisterna magna and spinal subarachnoid space, and from here by further manipulation of the head it can be used to test the patency of the pathways from the basal cisterns to the convexity of the brain.

In most cases of infantile hydrocephalus without obstruction in the ventricular system there is usually found to be a block of the basal cisterns at the level of the tentorium cerebelli, so that the air will not enter the cerebral sulci.

Lumbar encephalography is normally used only to demonstrate the fourth ventricle and aqueduct either when the air has passed too rapidly through them into a capacious cisterna magna or to confirm the diagnosis of aqueduct stenosis. The latter condition may be associated with basal cistern block which can then only be shown by lumbar encephalography.

Bubble ventriculography carried out in the way described is quite sufficient to show the degree of dilatation of the lateral ventricles. It will also show if they are displaced. It does not allow them to be explored completely. In particular their trigones are not necessarily shown and there is not usually sufficient air to obtain complete filling of the temporal horns. A choroid plexus papilloma may be overlooked if this method is used. Only therefore if the condition is suspected either on clinical grounds prior to investigation, or when there was an unexpected reaction to a bubble ventriculogram, perhaps in the presence of papillœdema and an abnormal cerebrospinal fluid, will the appropriate radiological technique be adopted to show the tumour.

In order to outline a tumour arising in the trigone or temporal horn of a dilated lateral ventricle it is necessary to replace as much of the ventricular cerebrospinal fluid as possible with air. Each lateral ventricle is examined separately, films being taken with the head supine, prone and lateral with the appropriate lateral ventricle uppermost. With the head in the lateral position both lateral and antero-posterior projections are

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used. In turning the head from supine to prone the lateral ventricle under investigation is kept uppermost, and the vertex is kept high to prevent loss of air from the lateral ventricle into the third and fourth ventricle. Manipulation of air into each temporal horn may be necessary. Finally the remainder of the cerebrospinal fluid pathway is demonstrated as already described.

The degree of hydrocephalus is sometimes not very great and the lateral ventricles are not usually displaced. The tumour may be shown as a filling defect in the region of the trigone but if it is pedunculated, as its specific gravity is greater than that of cerebrospinal fluid, it will not float on the fluid. With the head in the prone position it will sink into the body of the ventricle and only its surface may be visible where it projects into the air in the trigone. It is therefore necessary to search all the films very carefully for such a shallow filling-defect. Similarly with the head in the lateral position the tumour may fall away towards the medial wall of the ventricle. It is however seldom desirable or even possible to inject sufficient air into the lateral ventricles through the fontanelle or burr hole to outline the whole surface of the tumour.

In 2 of the 5 cases, where the tumour extended into the temporal horn its lobulated surface was outlined by air. This air had the appearance of wide cerebral sulci and in the first of these cases it was concluded that the air was, in fact, in sulci and that there was no evidence of block. In the second case the significance of this appearance was appreciated and the air was shown to be in the temporal lobe and not on the surface of the brain. The air was actually situated in clefts in the lobulated

TABLE II.—RADIOLOGICAL FINDINGS

| | *Skull* | | | *Pneumography* | | | | |
|---|---|---|---|---|---|---|---|---|
| *Case* | *Hydro-cephalus* | *Suture diastasis* | *Calcifi-cation* | *Small or large volume* | *Degree of hydro-ceph.* | *Smooth filling defect* | *Air filled clefts on tumour* | *Basal cistern block* |
| 1 | Moderate | + | — | Small | Severe | — | — | + |
| 2 | Moderate | + | — | Small | Moderate | — | + L. temporal | + |
| 3 | Moderate | + | — | Small | Moderate | + | — | + |
| 4 | Slight | + | — | (1) small (2) large | Moderate | + R. trigone and body | — | + |
| 5 | Moderate | Very slight | — | (1) small (2) large | Very severe | — | + L. temporal | + |

surface of the tumour. Its appearance is similar to that found in intracerebral epidermoids (cholesteatoma) and often thought to be diagnostic of this condition. The temporal horn is usually more dilated and distorted by the tumours lying within it than the remainder of the ventricle or the opposite temporal horn. The third and fourth ventricles are usually dilated and there is likely to be evidence of basal cistern block.

The radiological findings in the 5 cases reported are summarized in Table II.

Carotid angiography had not been performed in any of these cases. It is probable that these tumours could have been shown as has been reported in the case of an adult presenting with subarachnoid hæmorrhage (Ernsting, 1955).

*Surgical Technique*

The choroid plexus papilloma of the lateral ventricles usually lies in the region of the trigone. It is therefore possible to remove the tumour through a posterior parietal incision.

A twenty to thirty degree tilt of the body head uppermost assists in reducing the intracranial tension. A rectangular scalp flap of moderate size, approximately $7 \times 5$ cm. is turned with its base away from the vertex. The bone flap in infants may be cut with strong scissors.

If a reduction of tension is required before the dura can be safely incised, the lateral ventricle may be tapped. This should be performed with great care as the needle may impinge upon the tumour and cause fresh bleeding. A cortical incision is next made into the ventricle using suction after superficial coagulation. If the ventricle is large the cerebral tissue may require continuous support with malleable retractors.

Ideally the tumour should be removed intact. In our experience, however, it is seldom possible to identify and deal with the vessels at the base of the growth until much of the latter has been removed by rongeur and suction. As soon as possible during the procedure the remainder of the ventricle should be isolated from the tumour region by lintine packs, in order to limit the spread of blood and tumour cells. The tumour base at the glomus of the choroid plexus is finally dealt with by applying tantalum clips to the vessels and coagulating any plexus that may remain. The possibility of secondary adherence of the growth to neighbouring ependyma should be borne in mind and areas of adherence should be sought after removal of the main tumour. The ventricle is lastly thoroughly flushed with saline of body temperature before closing the wound, in order to minimize the risk of seeding.

## Discussion

The majority of cases of choroid plexus papilloma situated in the lateral ventricles have hydrocephalus to some degree. Many of these are

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regarded as cases of communicating hydrocephalus until extensive investigation, surgical exploration, or post-mortem examination reveals the true diagnosis. It is likely that many more cases remain undetected, for hydrocephalic children, following incomplete investigation and unsuccessful treatment often die at home or in long-stay hospitals where a post-mortem examination may not be performed. Thus, this type of tumour situated in the lateral ventricle may well be more common than the published series suggests. The danger of performing shunting operations on incompletely investigated cases of hydrocephalus cannot be stressed enough. Not only will this lead to such cases being missed, but also inevitably to the failure of the shunting procedure.

The hydrocephalus associated with these lateral ventricular choroid plexus papillomata has at least two chief causes, namely over-secretion of cerebrospinal fluid and hæmorrhage from the vascular tumour. Occasionally the tumour may obstruct the foramen of Monro (Fincher, 1934) perhaps intermittently, leading to a unilateral hydrocephalus. A membrane often formed in association with the papilloma perhaps as a result of a previous hæmorrhage may block the outflow from the whole or part of a lateral ventricle (Rand and Reeves, 1940; Dandy, 1934; Friedman and Solomon, 1936). On the other hand, extensive seeding of the tumour in the subarachnoid space might possibly produce a subarachnoid block (Gillis and di Profio, 1956).

The histological appearance of these tumours resembles that of a normal choroid plexus very closely though the villi are usually much more vascular and the epithelium generally more cylindrical and active in appearance. That these tumours are functionally active would therefore not be surprising and by virtue of their very great bulk, secrete excessive amounts of cerebrospinal fluid. Such over-secretion has been demonstrated quite convincingly in a number of instances (Ray and Peck, 1956; Braunstein and Martin, 1952; Smith, 1955; and Johnson, 1958, and others). The C.S.F. absorbing mechanisms are probably unable to deal with this excessive fluid which then accumulates and produces the symmetrical dilatation of the ventricular system.

The great vascularity of these papillomata is responsible for many of the clinical features. Hæmorrhage from them, which occurs at the slightest provocation was experienced at operation. This would explain the xanthochromic cerebrospinal fluid with its raised protein and, in many instances, increased cell content which seems to be a fairly constant feature. Hæmorrhage into the cerebrospinal fluid probably accounts for the associated basal cistern block (Laurence, 1959) seen in all 5 of our cases and in many of those previously reported. This block added to the over-secretion of fluid would certainly account for the rapidly progressive hydrocephalus. Hæmosiderin deposits in the ependyma suggest that these hæmorrhages though small may well have been occurring for some

considerable time. Further, it is likely that the acute episode regarded as a cold, bilious attack or other condition which led to admission to hospital in 4 of our 5 patients, was caused by a hæmorrhage from the tumour which was almost certainly present for a considerable time previously. In many of the reported cases a membrane, which is probably organized hæmatoma or a gross blood clot, was found at operation or autopsy (Guérard, 1833; Kristen, 1948; Sandison, 1956).

Papillœdema in this condition which is not often seen in the usual type of hydrocephalus of early childhood (Laurence, 1960) can probably be accounted for by the slightly later onset, when the skull is more formed and sutures more united. The importance of this papillœdema, though mentioned was not sufficiently stressed in a recent review by Matson and Crofton (1960). Further, the hydrocephalus, once a basal cistern block has been established would progress more rapidly by virtue of the over-secretion of the cerebrospinal fluid.

The severe reaction following ventriculography is, however, more difficult to explain. Whether this rapid progress is precipitated by the sudden release of intracranial tension, resulting in a great increase in the cerebrospinal fluid production or additional hæmorrhage from the tumour, or by some other cause, is a matter for conjecture. Whatever the mechanism, it would almost certainly have to account for the widespread subependymal and corpus callosum hæmorrhages found in 2 of the first 3 cases.

It is thus possible to explain the basis of most of the clinical and diagnostic features of these tumours, which have always proved such a diagnostic difficulty. Understanding some of the underlying mechanisms may help in the more rapid recognition of cases in the future.

## Summary

Five cases of choroid plexus papilloma situated in the lateral ventricles of children are reported. Although the diagnosis has always been difficult, hydrocephalus associated with moderate papillœdema, unusual in young children, and cerebrospinal fluid under severely raised tension and with raised protein and cell content should arouse the suspicion that such a tumour might be present. This suspicion should be heightened when a very severe reaction to air studies occurs.

The final diagnosis rests on ventriculography, more extensive than the usual "bubble" ventriculogram employed in hydrocephalic children, which will show a symmetrical hydrocephalus often severe, due to a basal cistern block, and outline part of the tumour. The techniques for this and the surgical removal, which should follow swiftly, are given.

Some clinical implications of the hydrocephalus, caused mostly as a result of over-secretion and bleeding into the cerebrospinal fluid from the high vascular tumour, are discussed.

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This tumour, more common in children than in adults, is at least theoretically benign and it is felt, that with more certain diagnosis and speedier treatment better results, than have been achieved in the past, can be obtained.

ACKNOWLEDGMENTS

For their helpful co-operation we wish to thank our colleagues, especially Dr. M. Bodian and Mr. Wylie McKissock, for the photographs of specimens Mr. Derek Martin, for the photomicrograph Mr. T. J. Cooke, and for permission to publish figs. 1 and 3, the Editors of the Annals of the Royal College of Surgeons and of the Ciba Symposium on the "Cerebrospinal Fluid." One of us (K. M. L.) is indebted to the Research Committee of the Hospital for Sick Children for support while some of the work was being carried out.

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FIG. 1.

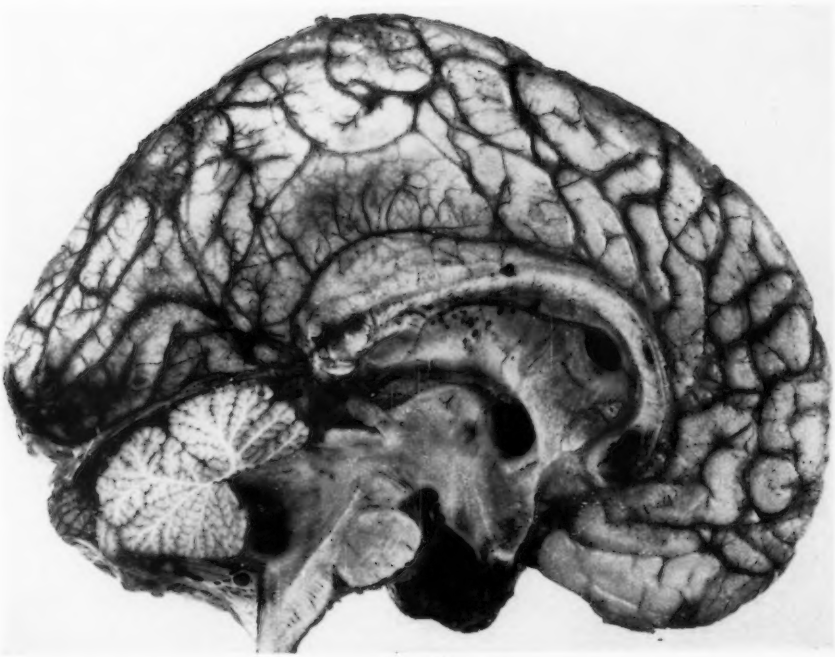

FIG. 2.

*To illustrate article by K. M. Laurence, R. D. Hoare and K. Till.*

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PLATE LXXVII

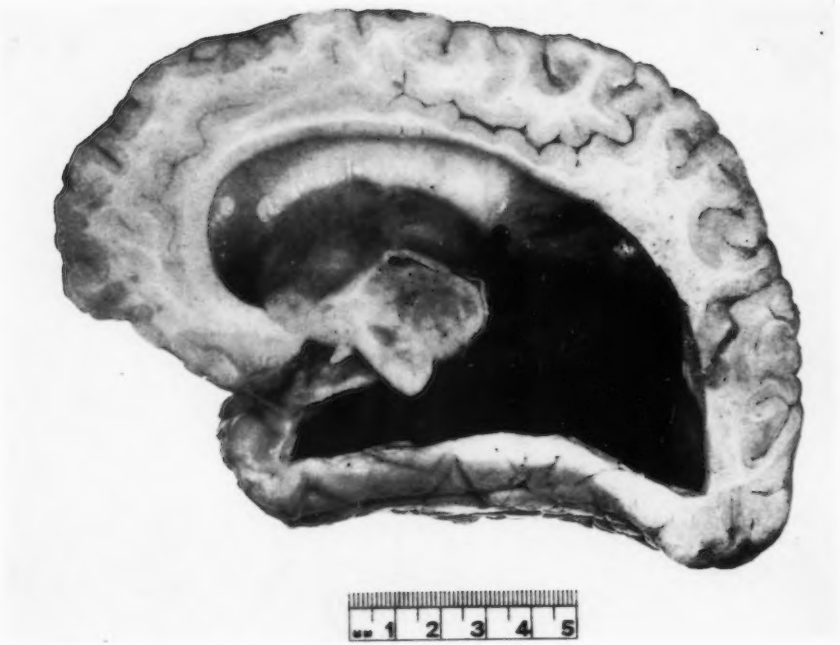


FIG. 3.

*To illustrate article by K. M. Laurence, R. D. Hoare and K. Till.*

PLATE LXXVIII

FIG. 4A.

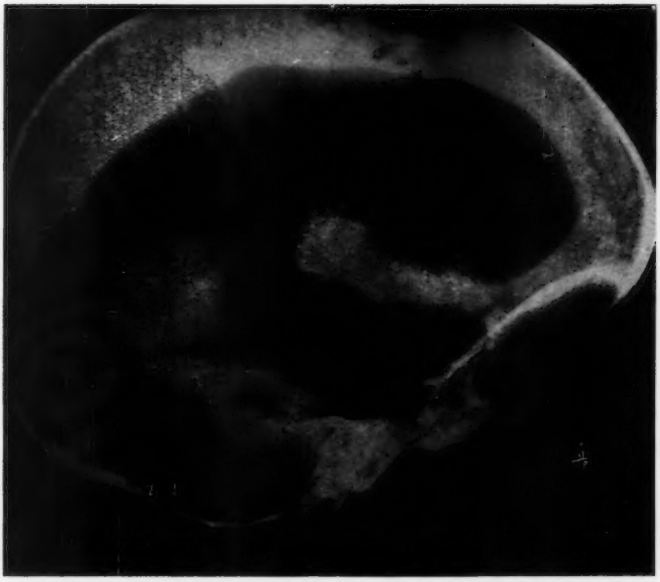

FIG. 4B.

*To illustrate article by K. M. Laurence, R. D. Hoare and K. Till.*

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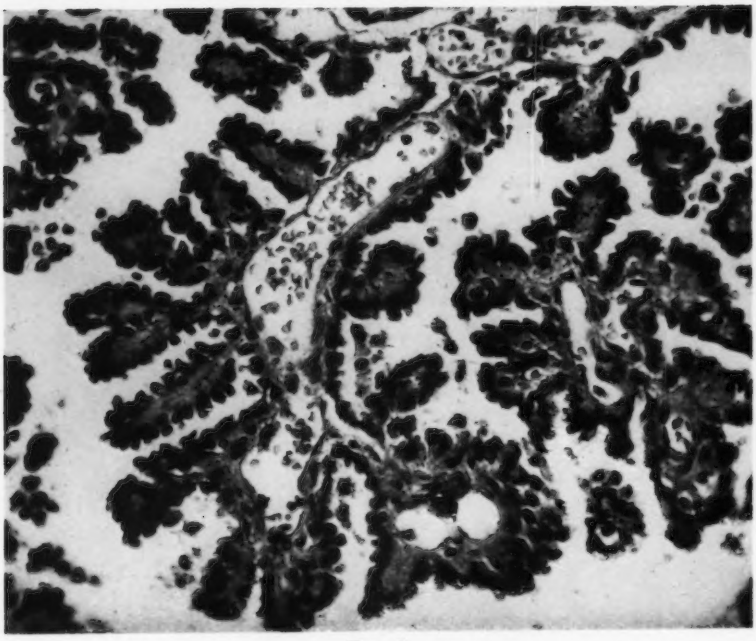

FIG. 5.

FIG. 6.

*To illustrate article by K. M. Laurence, R. D. Hoare and K. Till.*

FIG. 7.

FIG. 8.

*To illustrate article by K. M. Laurence, R. D. Hoare and K. Till.*

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FIG. 9.

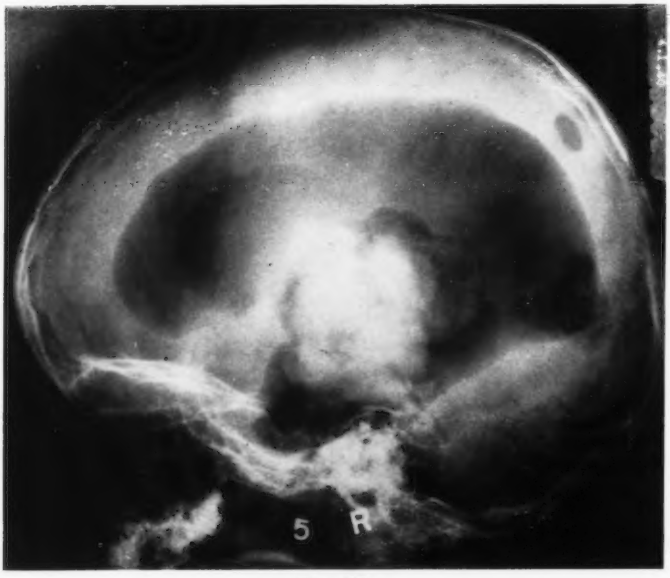


FIG. 10.

*To illustrate article by K. M. Laurence, R. D. Hoare and K. Till.*

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## LEGENDS FOR PLATES

### PLATE LXXVI

FIG. 1.—A parasagittal section of the brain of Case 1 to show the large choroid plexus papilloma in posterior portion of the markedly dilated lateral ventricle. The tumour is attached to the glomus of the choroid plexus anteriorly and to the ventricular wall by a secondary glial stalk posteriorly. Subependymal hæmorrhages are profuse.

FIG. 2.—Hemisected brain of Case 1 to show the severe symmetrical dilatation of the ventricular system, the hæmorrhages into the corpus callosum, and the cerebellum indented inferiorly by a large cisterna magna.

### PLATE LXXVII

FIG. 3.—Parasagittal section of the cerebrum of Case 2 to show the large congested choroid plexus tumour in the posterior and inferior horn of the right lateral ventricle.

### PLATE LXXVIII

FIG. 4A and B.—A parasagittal section of the brain of Case 3 to show the rounded cauliflower tumour in the posterior horn of the right lateral ventricle. A number of terminal subependymal hæmorrhages are present. A post-mortem radiograph of the right side of the skull after drainage of the C.S.F. shows the tumour and the degree of hydrocephalus clearly.

### PLATE LXXIX

FIG. 5.—A photomicrograph of the tumour of Case 3 (hæmatoxylin and eosin ×340).

FIG. 6.—Hemisected skull of Case 3 demonstrating severe dilatation of the third and fourth ventricles. Fine fibrous strands traverse the hugely dilated cisterna magna, while the interpeduncular cistern is so greatly expanded as to elevate the floor of the third ventricle, elongate the pituitary stalk and optic nerve and flatten the pituitary gland.

### PLATE LXXX

FIG. 7.—The prone lateral film of the ventriculogram of Case 3. The posterior surface of the tumour is shown just breaking the horizontal air-fluid level in one lateral ventricle.

FIG. 8.—Lateral film of ventriculogram (right lateral ventricle uppermost) of Case 4. A faint but definite oval filling defect is present in the body and trigone of the ventricle. Its presence is confirmed by the antero-posterior film taken with the head in this position.

### PLATE LXXXI

FIG. 9.—The anteroposterior ventriculogram of Case 5. The lateral ventricles are dilated. The surface of the tumour is partly outlined by air in the left temporal region.

FIG. 10.—The lateral ventriculogram of Case 5 (left lateral ventricle uppermost). The tumour is more completely outlined, the dilated tip of the temporal horn is visible with the anterior pole of the tumour projecting into it.

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# PARKINSONISM-DEMENTIA COMPLEX, AN ENDEMIC DISEASE ON THE ISLAND OF GUAM

## I. CLINICAL FEATURES

BY

ASAO HIRANO,[1] LEONARD T. KURLAND,[2] ROBERT S. KROOTH,[2] AND SIMMONS LESSELL[2]

### INTRODUCTION

GUAM and the other Mariana Islands in the Western Pacific Ocean represent a geographic isolate with a phenomenal incidence of fatal neurological diseases. The best known of these ailments among the 38,000 indigenous Chamorro people is amyotrophic lateral sclerosis (ALS), which accounts for about 10 per cent of the adult deaths, or about 100 times the death ratio reported for any other population (Arnold, Edgren and Palladino, 1953; Koerner, 1952; Kurland and Mulder, 1954; and Kurland, 1957).

A form of Parkinsonism with dementia has also been endemic in this population for at least several decades and perhaps for centuries; but only in the last two years has a systematic effort been made to describe its clinical and pathological features and to determine its genetic and epidemiologic relationship to ALS. In 1954, Mulder, Kurland and Iriarte reported that, in the course of their early studies on Guam they observed 22 patients with Parkinsonism, many of whom appeared confused or demented; these cases were thought to be "postencephalitic" disease. According to the reports at the Neurological Research Center on Guam, 21 additional cases with Parkinsonism, most of whom also had dementia, were observed during 1957 and 1958.

A case register was established in late 1958 to facilitate a long term prospective genetic investigation of ALS and Parkinsonism, and with the arrival of one of us (A. H.) on Guam in 1959, a concerted effort was made

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to provide a detailed clinical and pathological description of the cases. It soon became apparent that although a few patients had clinical features of Parkinson's disease, the large majority had a combination of a severe progressive dementia with extrapyramidal disease (Parkinsonism-dementia complex) and, in an appreciable number of patients, motor neurone involvement as well.

In the relatively small population of Guam during the year prior to October, 1960, more than 140 patients (including 30 who were necropsied) were observed for ALS, Parkinsonism-dementia complex or evidences of both disorders.

The purpose of this paper is to present a clinical description of 47 selected Parkinsonism-dementia cases and to discuss their relationship to ALS and to "presenile" dementia and Parkinsonism in other populations. Statistical and genetic data will also be presented. A companion paper deals with the pathological features of 17 autopsied cases of Parkinsonism-dementia. Later reports will consider the epidemiology and genetics of Parkinsonism-dementia based on extensive population surveys currently under way.

The clarification of the diseases on Guam may have far wider implications for neurology than the control of these ailments among the Chamorros alone. Any success in these studies will be due in great measure to the unique conditions of remoteness of this geographic isolate and the co-operation of its population.

To facilitate the clinical description, the cases have been divided into three groups:

I. Parkinsonism-dementia complex.

II. Parkinsonism-dementia and clinical evidence of upper motor neurone disease.

III. Parkinsonism-dementia with clinical evidence of upper and lower motor neurone disease (ALS).

On the basis of the latest examination reports, 30 patients were classified in Group I, 8 in Group II, and 9 in Group III (Table I). Almost all patients in Group I had bilateral hyperactive muscle stretch reflexes which were often severe enough to suggest pathological changes. Although this division of the syndrome may prove to be artificial, only patients with the Babinski sign, unilateral hyperactive reflexes, or other unequivocal evidence of upper motor neurone involvement were included in the Groups II and III.

## Case Reports

Group I.—Clinical evidence of Parkinsonism and dementia: 30 cases.

*Case* 1.—F. S. M. (Born: 1902). This Chamorro housewife was first seen at the Neurological Research Center on April 2, 1958, with a chief complaint of weakness of both hands of six months' duration. The patient's family stated that she had



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been slow in talking and moving and that her memory began to fail during 1956; these symptoms had become particularly apparent by January 1958. She dropped things frequently and was incapable of skilled household work. No history of a serious febrile illness or severe headache which would suggest encephalitis could be elicited. One of her sisters had died of ALS. Initial neurological examination revealed a striking absence of spontaneous movement; there was mask-like facies, stooped posture and slow gait. She did not swing her arms unless attention was called to this. A generalized increase in muscle tone was accompanied by slight cogwheel rigidity on pronation of hands bilaterally, but there was no tremor. Alternating and associated movements were impaired, but there was no ataxia. The patient appeared depressed; mentation was slow and memory was poor especially for recent events. She answered questions hesitatingly but was unable to recall the question or the answer a short time later. Her speech was slow and monotonous and her voice was low-pitched. Muscle strength was normal and there was no atrophy or fasciculations. Touch, superficial pain, deep pain, vibratory and position senses were intact. Extraocular movements, including convergence, pupillary responses and fundi were normal. The remainder of the physical examination was unremarkable. Blood pressure was 120/80. A hemogram, blood sugar, blood urea nitrogen, serological test for syphilis, routine urinalysis, and x-ray films of the skull and chest were within normal limits. Lumbar puncture: cerebrospinal fluid (CSF) initial pressure, cell count, total protein, sugar and chloride were normal and the Wassermann reaction was negative.

In the ensuing months the patient deteriorated gradually and required continual observation by her family. Neurological examination in her home on September 17, 1959, revealed the following: she could not reply coherently to simple questions, even when she was addressed in the Chamorro language. Her facial muscles exhibited an unnatural immobility and she constantly stared into space. There was an increased sebaceous secretion on the face and sialorrhœa. The patient spent most of her time sitting quietly in a chair, but she was able to walk a short distance without assistance. There was no resting tremor. Minimal cogwheel rigidity was noted at the left wrist. There was generalized weakness, but no muscle atrophy or fasciculations. The knee and ankle muscle stretch reflexes were hyperactive, snout reflexes were present but the Babinski sign was absent.

Electroencephalogram (EEG) on November 12, 1959, showed a background pattern of irregular eight to nine per second activity of moderate voltage. The record was poorly organized because of frequent moderate to high voltage five to seven per second slowness which occurred without specific localization. A period of hyperventilation was attempted without success because of her mental deterioration. There were no paroxysmal activities.

When she was examined on December 16, 1959, further deterioration was obvious and she was in a vegetative condition. There was still no tremor, and cogwheel rigidity was felt only in her left wrist; there was no Babinski sign and focal muscle atrophy was absent. When last observed in August, 1960, the patient was helpless, bedridden, almost immobile and in a terminal state. At no time during the course of illness were oculogryal spasms observed.

*Case* 2.—A. C. P. (Born: 1897). This Chamorro farmer was unable to work after 1956, because of "tiredness." Prior to his first hospitalization at the Guam Memorial Hospital (G.M.H.), December 19, 1957, the patient's family had noted progressive slowness of his mental and physical ability, and a slight resting tremor of the right hand. Examination revealed a well-nourished, well-developed man who leaned forward as he walked with short steps. He had a blank facial expression, stooped

posture, mild resting tremor of the right hand, and cogwheel rigidity of the right arm. During the course of the examination it was necessary to repeat the same question two or three times before obtaining a delayed, barely audible reply. The physical examination was otherwise unremarkable, and the results of routine laboratory investigations were normal. The CSF was clear and the cell count, total protein, sugar, chloride and Wassermann reaction were within normal limits. A diagnosis of Parkinson's disease was made.

On October 1, 1959, examination revealed that the patient spent most of his time sitting quietly in a chair. He had mask-like facies with constant staring and infrequent blinking. His posture and gait were typical of advanced Parkinsonism. He appeared confused and was unable to tell about his illness or give answers to very simple questions. Only after repeated questioning in the Chamorro language could he even recall the name of his village. Mild tremor was noted in the right index finger, thumb and in the tongue; there was slight cogwheel-like resistance at the elbows. There was no muscle wasting or fasciculations. Muscle stretch reflexes were hyperactive throughout. On the face-hand test, there was constant extinction of the hands. An EEG was taken on October 22, 1959; at this time the patient was still ambulatory and appeared adequately nourished. The record was abnormal, with a moderately slow background pattern with superimposed intermittent, five to six per second activity of moderate voltage (fig. 1).

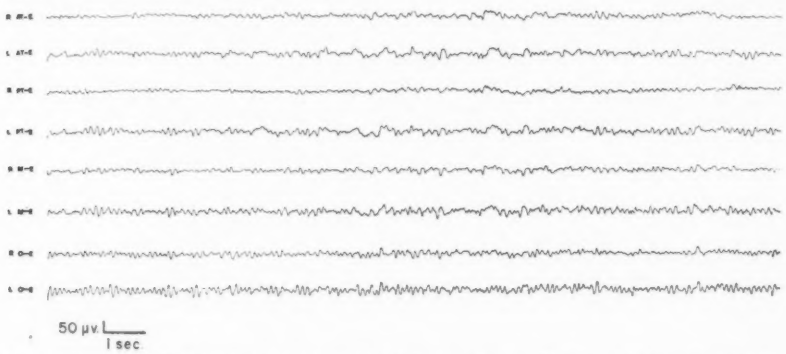


FIG. 1 (*Case* 2).—Parkinsonism with mental deterioration. The record shows moderate voltage and generalized slow activity.

Follow-up examination in June 1960 revealed further progression of the above symptoms and an increase in the tremor of the right hand.

Cases 3 to 30 were similar in onset and clinical course; their essential features are presented in Table I. More than one sibling of Case 3 (fig. 2, III) and Case 8 (fig. 2, I) was affected with ALS or the Parkinsonism-dementia complex. Case 9 was the wife of Case 30; Case 11 was a daughter of Case 12 and was the only patient in the present series with the onset of illness under 40 years of age.

EEG of Case 3 (fig. 3) taken on November 10, 1959, is illustrated to demonstrate the abnormality similar to that seen in Cases 1 and 2.

Thirteen of the patients in this group died before September 24, 1960. 12 of the 13 were autopsied and are reported in the companion paper of

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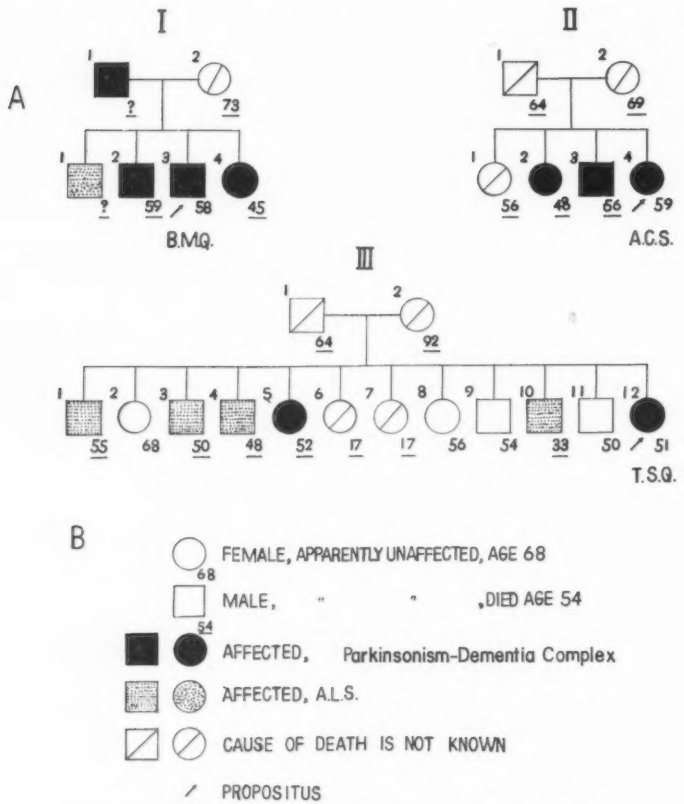


FIG. 2 (A) Pedigree of Cases 3, 8, and 31. (B) Pedigree key.

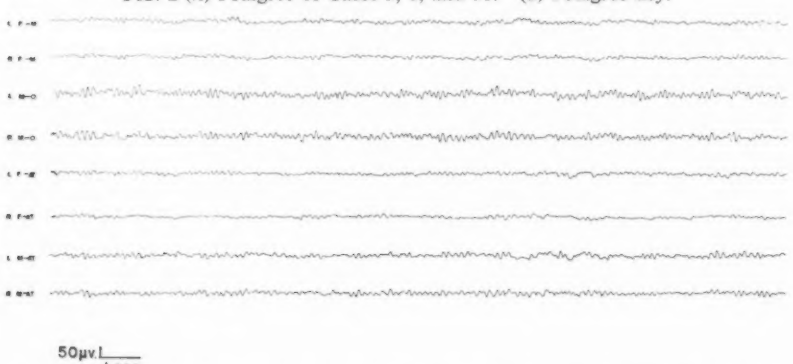


FIG. 3 (*Case* 3).—Parkinsonism with mental deterioration. The record shows low to moderate voltage seven to eight per second activity.

this series (Hirano, Malamud and Kurland, 1960). Case 25 is cited as an example.

*Case* 25.—V. C. P. (Born: 1907). This Chamorro man was in good health until early 1954, when he developed memory deficits, irregular sleeping habits, and had frequent periods of confusion during which he would wander aimlessly about the house. In July 1954, he was discharged from his job as a garbage collector because of "inability to do his work." The patient was first seen on October 16, 1957, at which time his family complained of his mental dullness and of occasional fæcal incontinence. The patient and his family denied any history of a similar illness in the family. The patient walked slowly, bent forward with a shuffling gait and with no swinging of the right arm. An intermittent tremor was present in the right hand. Cranial nerves were intact and no abnormalities were noted in the sensory examination. Muscle examination revealed fasciculations in the deltoids, but no atrophy. There was mild, generalized increased muscle tone with no cogwheeling phenomenon. Alternating movements were impaired, but the results of other cerebellar function tests showed no abnormality. Questions were answered quietly and appropriately, but he would "be talking nonsense to himself" frequently. He was disoriented for time. The blood pressure was 140/90. Blood serology, hæmogram, and routine urinalysis were normal. The chest X-ray showed "old healed tuberculosis." Skull X-rays were read as negative. The CSF findings were unremarkable. The diagnosis was "chronic brain syndrome with features of Parkinsonism." The patient was started on Artane, 2 mg., t.i.d., but it was discontinued shortly thereafter when he began to hallucinate. His final admission on December 9, 1958, was for overwhelming, disseminated pulmonary tuberculosis. In spite of vigorous antibiotic therapy, the patient expired on December 14, 1958. He is designated as Case 3 in the pathology paper (Hirano, Malamud and Kurland, 1960).

Group II.—Clinical evidence of Parkinsonism and dementia with upper motor neurone signs developing in the course of the illness: 8 cases.

*Case* 31.—A. C. S. (Born: 1900). This Chamorro housewife was examined for the first time on September 16, 1959, because of an eighteen-month history of tremor of the hands, forgetfulness and confusion of insidious onset. A sister and brother had died of a similar form of Parkinsonism (fig. 2, II). The family stated that the patient had had no significant febrile illness prior to the onset of her present illness. She had been treated for mild diabetes during the past four years, but was well-controlled with diet at the time of examination. Hypertension was noted in 1957 during an admission to the G.M.H. for a cholecystectomy. General physical examination revealed a blood pressure of 180/100, and no other abnormal physical signs aside from the neurological findings. The patient was co-operative, but her responses were slow and confused. There was memory loss, loss of orientation for time and place, acalculia and right-left disorientation. There was rhythmical tremor of the left forearm and hand, increased tone and cogwheel rigidity of all four extremities, most pronounced in the left arm; there was more weakness of the left arm, hand and fingers but no atrophy or fasciculations. The muscle stretch reflexes were exaggerated, more so in the upper limbs, and particularly on the left side. A palmomental reflex and Hoffmann's sign were more pronounced on the left side. The masked facies, the slow, shuffling gait and the impairment of associated movements gave a striking picture of Parkinsonism. There was flattening of the left nasolabial fold, but the rest of the cranial nerves tested satisfactorily and there was no sensory impairment. The EEG showed generalized moderate voltage slowness in range of theta activity (fig. 4).

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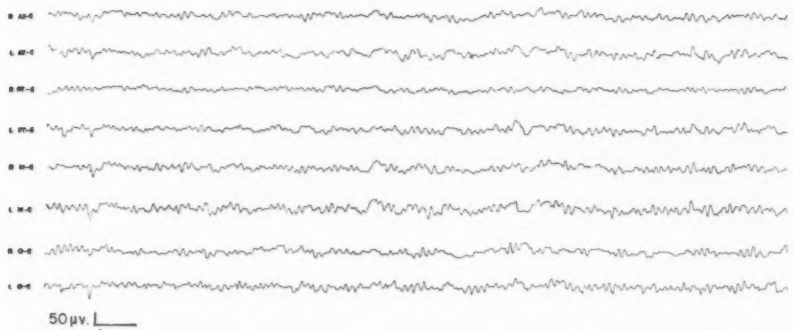


FIG. 4 (*Case* 32).—Parkinsonism with mental deterioration and pyramidal signs. The record shows moderate voltage generalized slow activity. The tracing is poorly organized.

Cases 32 to 38 presented neurological manifestations essentially similar to those of the above case as demonstrated in Table I. The symptoms and signs of upper motor neurone involvement including pathological reflexes were bilateral in 2 cases (Cases 34 and 36), while 3 others showed unilateral predominance; the right side was more affected in Cases 33 and 35, and the left side, in Case 32. Fig. 5 (Plate LXXXII) is a photograph of Case 33 and demonstrates mask-like expressionless face and stooped posture.

GROUP III.—Parkinsonism and dementia with ALS syndrome: 9 cases.

*Case* 39.—J. S. Q. (Born: 1917). This man, who was known to have mild diabetes, was examined in his home on November 18, 1959. His mother had died of ALS, and two of his brothers had died of a disease similar to his own. According to his family, about 1957 the patient developed an insidious and slowly progressive mental dullness. In March 1959 he was admitted to the G.M.H. after falling out of a tree, but he had suffered no apparent head injury in that fall. At that time, he was apathetic, and spoke to no one, including his own family. Occasionally a "pill-rolling" tremor of both hands was noted at rest, especially if he seemed tense. During the September, 1959 examination, he was disoriented as to time but was able to understand some of the simple questions asked in the Chamorro language. He gave only simple answers in a dysarthric voice. His face was mask-like; he blinked infrequently and stared vacantly into space. His appearance and posture resembled those of Parkinsonism, or, possibly, catatonia. His gait was unsteady with short steps, and there was an absence of arm swing. Associated movements were severely impaired. Rigidity was minimal and tremor was absent in the extremities; his tongue showed spontaneous tremor-like movements and may have been slightly atrophied. A palmomental reflex was present bilaterally, the jaw-jerk was brisk, and snout and sucking reflexes were present. Strength was impaired, particularly in the deltoid muscles but no definite wasting or fasciculations were detected. Except for absent ankle-jerks, the muscle stretch reflexes were hyperactive. A Hoffmann's sign was elicited on the left, and the plantar responses were equivocal on both sides. Sensory examination revealed no abnormality. When examined in his home one

A B

FIG. 5 (*Case* 33).—A and B, Mask-like, expressionless face and stooped posture.

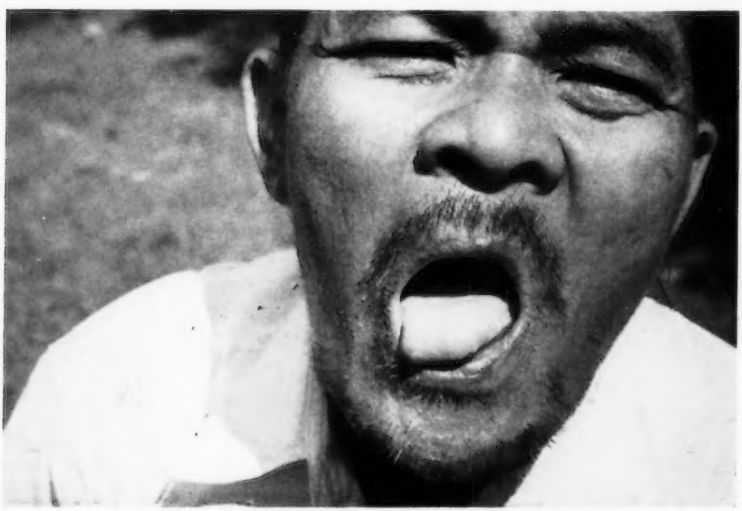

FIG. 6 (*Case* 39).—Early atrophy and slight deviation of tongue; patient is unable to protrude tongue beyond lower lip because of weakness.

*To illustrate article by Asao Hirano, Leonard T. Kurland, Robert S. Krooth and Simmons Lessell.*

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month later, further deterioration in his general condition was evident and there were fasciculations and atrophy of the tongue (fig. 6). When he was hospitalized in the G.M.H. on September 5, 1960, his facial muscles were paretic; there was cogwheel rigidity of all four extremities, and bilateral Babinski signs were noted. There was atrophy of the muscles in both forearms and the dorsal aspect of both hands. He died on September 23, 1960.

*Case* 40.—J. N. T. (Born: 1906). This Chamorro man was first seen on February 27, 1957, because of somnolence, weakness of the right arm and stiffness of both legs of three months' duration. The family stated that his memory had been failing for the past few years. For nine months he had had nocturnal hallucinations in which he conversed with a deceased friend. On neurological examination he walked leaning forward with a shuffling gait. There was no tremor. He appeared drowsy, apathetic, showed memory deficits for recent and past events and had a short attention span. His voice was soft and low-pitched. Slight cogwheel rigidity was present at the right elbow, and alternating movements were impaired. Fasciculations were noted intermittently over both forearms. The muscle stretch reflexes were brisk and Hoffmann and Babinski signs were present bilaterally. He was placed on Artane, 2 mg., t.i.d., but in three days' time he became so excited that the Artane had to be discontinued. In March 1957, the patient was found to have inactive rheumatic heart disease with mitral stenosis and benign prostatic hypertrophy, in addition to his neurological problems. Routine laboratory studies of blood, urine and serology were normal at that time. In July, 1957, the patient was unable to continue his duties as a school janitor, because he had become "too slow" for the job. In August, 1957, he became more confused and the memory impairment became severe. His face was mask-like and his voice almost inaudible. Active palmomental and sucking reflexes were present bilaterally, and unsustained clonus was noted at both ankles. Tremor and cogwheel rigidity were absent. He continued to deteriorate, and expired on June 26, 1958. At the time the patient died, muscle wasting was noted in all extremities. The final clinical diagnosis was an organic mental syndrome, Parkinsonian syndrome, and ALS (Case 11 of the pathology report, Hirano, Malamud and Kurland, 1960).

*Case* 41.—J. Q. Q. (Born: 1905). This Chamorro man was admitted to the G.M.H. on May 8, 1956, because of mental and physical sluggishness and difficulty in speech which began insidiously about one year prior to admission. There was no family history of ALS. Examination revealed an obese, dull and drowsy man who was slow in both motion and speech. Blood pressure was 160/90. There was generalized hyperreflexia and bilateral Hoffmann's signs. The plantar responses were flexor. The patient was diagnosed as an organic mental syndrome of unknown ætiology. Laboratory tests at that time, including hæmogram, blood serology, blood chemistry, liver function tests, urinalysis, and stool examination for ova and parasites, were normal. The CSF findings were unremarkable. When readmitted nine months later on February 12, 1958, he was bedridden, incontinent of urine and fæces, had infected decubiti, and was moribund. The family had been unable to feed him because of his dementia and his difficulty with chewing and swallowing. The neurological report revealed that the patient had mask-facies, infrequent blinking, and drooling of saliva. His hands were held in a pill-rolling position and tremor was present in the upper extremities. There was rigidity of the muscles of mastication, facial expression, the neck, and limbs. Muscular atrophy was noted in the upper limbs and shoulder girdles, and fasciculations were observed in the face. His mouth could not be opened. Muscle stretch reflexes were absent, and there was no response to plantar stimulation. Sensory examination could not be carried out because of his inability to communicate.

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He appeared to be conscious; he stared at the examiner as the latter moved about the room, but there was no indication that he comprehended what was going on. Eye movements, pupillary reactions and funduscopic examinations were normal. Terminally, there was pyrexia of 105° F. and he died on February 16, 1958. The final diagnoses were chronic brain syndrome, ALS, and Parkinsonism (Case 12 of the pathology report, Hirano, Malamud and Kurland, 1960).

*Case* 42.—C. A. A. (Born: 1912). This Chamorro housewife had the onset of difficulty with the use of her hands and slowness of her gait about January 1958. Her family had noticed gradual, progressive deterioration of her mental and physical status some months prior to this date, but there was no history of an antecedent febrile illness. Neurological examination on September 17, 1959, revealed that she was a rather obese woman with mask-facies and a typical Parkinsonian gait. There was increased muscle tone in the upper and lower limbs, and slight but definite cog-wheel rigidity was present and was most pronounced at the wrists; there was no tremor. Alternating movements were slow but there was no ataxia. Cranial nerve and sensory examinations were normal. There was no obvious muscle atrophy; muscle stretch reflexes, including the jaw-jerk, were hyperactive. The palmomental reflex and a Hoffmann's sign were present on the right side. There was no clonus. The plantar responses were equivocal on both sides. Despite her deterioration, the patient was still able to count one to ten and ten to one, and could give the date and her address in the Chamorro language. The EEG taken on November 10, 1959, revealed generalized slowness of moderate voltage in the theta range (fig. 7). In

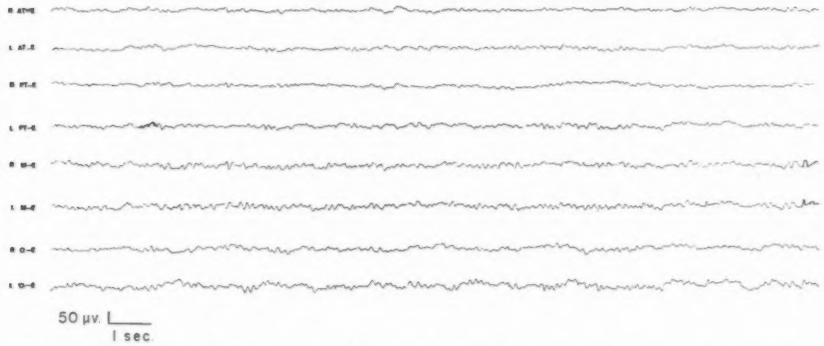


FIG. 7 (*Case* 42).—Parkinsonism with mental deterioration and amyotrophic lateral sclerosis syndrome. The record shows moderate amplitude generalized slowness.

the ensuing three months, the patient deteriorated further and was almost confined to bed at the examination on December 16, 1959. In addition to the neurological findings of the earlier examination, Hoffmann and Babinski signs were elicited on both sides. There was now atrophy of her hypothenar and other intrinsic hand muscles and fasciculations of the hands and forearms. The patient progressively deteriorated and died on April 30, 1960 (Case 13 of the pathology report, Hirano, Malamud and Kurland, 1960).

Cases 43 to 47 demonstrated essentially similar clinical features; namely, in addition to Parkinsonism with dementia, the ALS syndrome developed in the course of the illness.

## Analysis of Data

*Race.*—Although there is a sizeable Caucasian and Filipino population on Guam, all 47 cases occurred among the Chamorros. One patient (Case 46) had a Chamorro mother and a Filipino father.

*Distribution of cases.*—Systematic surveys of the population on Guam have been feasible in only a few villages. However, frequent contact with local public health nurses and commissioners who generally know their villagers well has served as a satisfactory case finding resource on a continuing basis for several years. The number of cases and consequently the prevalence rates in the small populations of the villages can be expected to fluctuate somewhat by chance. However, the available data strongly suggest that the distribution of cases of Parkinsonism-dementia complex is similar to that for ALS on the Island (Kurland and Mulder, 1954). The prevalence tends to be greatest in the villages which are more distant from the urban centre of the Island and is greatest in those villages in which the economy is predominantly agricultural.

*Age at onset.*—The age range was 32 to 64 years with a mean of 52 years for those providing a reasonably accurate date of onset. The array of ages is given in Table I. This differs from the reported ages of onset of Parkinsonism in the population of Rochester, Minnesota, where it averaged about 59 years in the "idiopathic" group and about 70 years in the group with recognized arteriosclerosis (Kurland, 1958).

*Sex.*—Although both sexes are affected, there is a preponderance of males in this series (36 males: 11 females). This contrasts with the sex ratio described in the report by Kurland (1958) in which there is essentially no difference by sex for idiopathic or Parkinsonism with recognized arteriosclerosis.

*Familial aggregation of cases.*—The family history was positive for ALS or Parkinsonism-dementia in 17 of the 47 cases, but this familial incidence must be considered as a minimal value. It was not always possible to obtain complete and accurate pedigrees of families on Guam because of the uncertainty of some family relationships, the near absence of written records due to destruction of church and civil archives during the second World War, the lack of medical information about progenitors and the reticence of many in the population to discuss affected relatives because of the stigma the Chamorros frequently associate with ALS.

Eight of the patients had a family history of ALS. These were a sister of Case 1, four brothers of Case 3, the father of Case 4, a brother of Case 8, the mother of Case 22, a sister of Case 34, the mother of Case 39, and a brother of Case 43. Ten patients had a family history of "Parkinson's disease": a sister of Case 3, a brother of Case 7, the father, a brother and a sister of Case 8, the father of Case 11, the daughter of Case 12, a brother of Case 17, a brother of Case 28, a brother and a sister of Case 31, a

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brother of Case 37, and two brothers of Case 39. In four instances (Cases 3, 8, 31 and 39) more than three of the family members were affected by either ALS or Parkinsonism-dementia complex or by both. Pedigrees of Cases 3, 8 and 31 are illustrated in fig. 2. In Case 8 the eldest brother had died of ALS, and the father and two other brothers had died of Parkinsonism-dementia complex. Everyone in the immediate family of this patient was affected except for the mother, and the cause of her death is unknown (fig. 2, I). In Case 31 an elder brother and an elder sister had died of a disease similar to that of the patient; three out of four children were affected in this family. The cause of death of the eldest daughter at the age of 56 years is unknown (fig. 2, II). The family history of Case 3 is also remarkable. Her parents died of unknown causes. They had twelve children, of whom six were affected either by ALS or by "Parkinson's disease." All of them had already expired except for our index case. The cause of death at age 17 years of two other twin sisters was unknown (fig. 2, III). In Case 39 the mother had died of ALS and two brothers had died of an illness similar to that of the patient. Cases in the same sibship generally had their onset at least a few years apart; aside from Cases 11 and 12, one or more decades intervened between the onset of illness in members of different generations of the same family.

In view of the exceedingly high incidence of ALS and Parkinsonism-dementia complex in the population, some degree of familial aggregation of cases can be expected by chance. In the absence of carefully controlled studies it is impossible to be sure from the available data that the degree of familial aggregation of the cases described is on a genetic rather than on an environmental or fortuitous basis. A more systematic and extensive genetic study which was originated in 1958 and was designed to answer this question, is still in progress.

*Onset.*—The mode of onset is always insidious and in all of the cases the illness is noted by their families rather than patients themselves. Although our experience differs from that in the report by Mulder, Kurland and Iriarte (1954), no clear history of preceding encephalitis, meningo-encephalitis or other significant febrile illness was obtained.

*Symptoms and signs.*—All of these patients showed a striking akinesia and a mask-like expressionless face with "reptilian stare" (fig. 5). Their stooped posture and slow and shuffling gait greatly resembled those of classical Parkinson's disease. Co-ordination, alternative movement and skilled actions were very poor. Generalized slowness, poverty of movement and loss of associated movements were among the main characteristics. In Parkinsonism, rigidity of muscles and a coarse tremor are the outstanding features, but the flexion posture and loss of swing of the upper extremities in gait constitute the most evident parts of this syndrome

since the tremor and the rigidity may be absent (Brock, 1953). Many of the 47 patients had been first diagnosed as "Parkinson's disease" by various previous examiners, and it is true that they had the Parkinsonian syndrome as one of the main features. However, all the patients demonstrated mental deterioration; the nature of extrapyramidal manifestations would appear to differ in a uniform way from that of the more commonly observed type of Parkinson's disease. In addition, unequivocal upper motor neurone signs or the ALS syndrome were evident in over one-third of the patients.

(*a*) *Tremor and Rigidity*

It is of interest that tremor is not a major characteristic of any of the cases. Although 32 of the 47 patients had tremor, it was of mild or moderate degree. In some patients it would be seen only when the patient was excited, and usually with action of the limb rather than with the limb in repose. In several of the patients, tremor was seen only in a hand or in the fingers alone; in some cases it was also present in the eyelids or tongue. Tremor of the head, which is frequently present in senile tremor was not seen in any of the cases. In no case, even those which were far advanced, did tremors involve the entire arm or leg in such a manner that they shook the entire body. The tremor was in abeyance during sleep. Fifteen of the patients did not have tremor or any other involuntary movement at rest or during activity.

From the appearance of their faces and postures, one would expect to find severe rigidity and increased tonus of the extremities in these patients. However, there was no appreciable rigidity in 28 of the patients. Extremities were even somewhat flaccid in 7 of them, and minimal to mild degrees of increased tonus or cogwheel feeling could be demonstrated only by careful attention in the 21 of the 28 patients.

In 19 of the 47 patients definite increased muscle tonus, rigidity and cogwheel resistance were present in one or more extremities. However, these were of a much less degree than might be expected from the overall appearance of the patients. In a few patients the extremities were rigid due to contractures produced by long-term confinement to bed or due to their sitting immobile for many hours. In some of the terminal patients the jaw was tightly clenched.

(*b*) *Mental Deterioration*

There is a history of mental slowness and poor memory in all the patients although the family rather than the patient was aware of this change. Thinking gradually became sluggish, comprehension less accurate, and the patients became slow, inefficient in their work, lacked initiative and at times went unclothed or otherwise conducted themselves in a socially inappropriate manner. They tended to be apathetic and

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indifferent. Depression was a common finding among them, and this was often in contrast to their former gay and talkative manner. For a few of the patients there was also history of hallucinations, usually associated with old friends and past events. In advanced cases of Parkinson's disease slow and thick speech can be expected, but in these cases there was clear deterioration rather than an inability to communicate, and the change of mental picture was of an organic, and not of a functional, emotional or psychogenic type. There was disorientation for time, place and even for persons; there was memory impairment for recent and past events, and difficulty in simple calculations. Indeed, in many of the patients, the organic mental syndrome was the dominant clinical feature, while the Parkinsonian syndrome, though definitely present, was less conspicuous. Some of the patients might even be more accurately described as having "presenile" dementia with prominent Parkinsonian features. It is difficult to evaluate aphasia, apraxia, or agnosia in these patients due to the language barrier, as well as their mental deterioration. However, at least in the early stage, these features are not recognized in any of the cases. The patients became apathetic, mute, immobile, lacked spontaneity, and finally fell into a progressive vegetative state before some infection terminated life.

(*c*) *Motor Neuron Involvement*

In Parkinson's disease reflex changes are not often present; the muscle stretch reflexes may be difficult to elicit since the rigidity may reduce their amplitude. However, generalized hyperreflexia was found in almost all cases. There were 8 patients (Cases 31–38) in whom definite pyramidal signs developed during the course of the illness. In 5 patients (Cases 31, 32, 33, 35, and 37) this was unilateral and in 3 patients (Cases 34, 36, and 38) it was bilateral at the time of their last examination. In these cases definite localized muscle atrophy and fasciculations indicating lower motor neurone involvement were not apparent, although generalized cachexia appeared in many of the terminal cases. However, there were 9 patients (Cases 39–47) who presented unequivocal upper and lower motor neurone signs, namely the syndrome of ALS, but otherwise the clinical features were identical to those of patients who did not show motor neurone involvement. Clinically, the patients in group III showed cerebral, pyramidal and extrapyramidal as well as lower motor neurone involvement.

(*d*) *Other Neurological Findings*

Loss of vision was found in 4 patients (Cases 7, 22, 32, and 36) who had monocular post-traumatic blindness. Otherwise, pupils were normal in size and shape and reacted normally to light; gross visual fields in the earlier cases which could be tested appeared normal. There was no greenish yellow pigmentation or Kayser-Fleischer ring at the sclerocorneal

border. Eye movements were intact except for impairment of convergence. It was hard to be sure, however, whether the difficulty converging was a specific deficit or resulted from inattention related to mental deterioration. Cogwheel rigidity of the eye muscles was not observed in any of the patients, nor were there any with oculogyric crisis. The facial expression was fixed and placid in all the patients. Hearing remained intact. Speech became impaired. Our patients generally had low dysarthric voices, but the rapid enunciation of words, which is often found in Parkinson's disease, was not present in advanced stages. There was difficulty in swallowing; the patient showed a loss of interest in his surroundings, and became inattentive even when eating. In the later stage of illness, the patients tended to starve in spite of every effort by the family to feed them. Ultimately, some patients developed a tightly clenched jaw due to contracture of muscles of mastication and required tubal feeding. Tongue and palate movements were also impaired, but in only one case were fasciculations of the tongue noted. Tics, spasms and torticollis were not found in any of the cases.

Cerebellar dysfunction was not found. Bladder and bowel incontinence was noted only in the presence of advanced mental deterioration. Sensation was intact in all the cases. Drooling of saliva appeared in some patients as a result of impairment of the normal involuntary movements of the facial and pharyngeal muscles.

*General physical examination.*—Apart from the neurological examinations no consistent abnormality was noted on physical examination. Although hypertension was found in 3 cases (Cases 4, 24 and 31) there was no significant history or clinical evidence of vascular disease. Mild diabetes was discovered in 5 cases (Cases 4, 17, 31, 39 and 44), but recent surveys conducted by Kovacs (1959) suggest that the incidence rate for diabetes among Chamorro adults may be appreciably greater than that in other populations. Thus, the presence of diabetes in these 5 patients may be coincidental; however, the question of an ætiological relationship between diabetes and the neurological syndrome among the Chamorros is still under study. A history of trauma was elicited in 5 cases, but this was either an unrelated accident occurring many years before the onset of illness (Cases 17, 22, 32 and 36) or an accident resulting from the neurological disability (Case 39). Chronic eczematous dermatitis was present in 2 cases (Cases 19 and 34). Pellagra was considered in the differential diagnosis of the neurological disorders in these patients, but the appearance and location of the skin lesions were not those of pellagra. The lack of significant gastrointestinal symptoms and also the uniform pattern of the neurological signs do not suggest pellagra in our cases; furthermore, vitamin B complex and nicotinic acid failed to have any effect on the course of the illness.

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A past history of significant alcoholism was not found among our cases. Clinical symptoms and signs of the liver damage were not found, and only one patient (Case 32) had had a cholecystectomy due to cholelithiasis.

*Laboratory data.*—Urinalysis, hæmatological studies, blood chemistry, blood serology and examination of the stool for ova or parasites were all unremarkable. Liver function, when tested, was normal, and the microscopic examination revealed no abnormality in the autopsied cases. X-ray studies of the chest and skull were normal. The diagnoses of the 5 mildly diabetic patients were based on findings of glycosæmia and the results of a glucose tolerance test. Lumbar puncture and examination of cerebrospinal fluid including sugar, total protein, chloride, serology and cell count were all within normal limits. Histochemical studies on skin biopsies in 4 cases revealed that 2 had changes similar to that noted in ALS (Fullmer, Siedler, Krooth and Kurland, 1960); further histochemical studies are in progress. Electroencephalograms were recorded in 12 patients and all of them showed the following abnormality: The background pattern was characterized by generalized eight to nine cycle activity of moderate voltage. There was also more specific abnormality with the occurrence of frequent intermittent moderate voltage slower activity ranging from five to seven per second, superimposed upon the background pattern. This appeared in all leads with some accentuation over the temporal areas. The degree of electrical abnormality seemed to be correlated with the degree of mental deterioration. None of the patients were comatose or malnourished, and the possibility that hypoglycæmia or drowsiness might be present was considered at the time of the examination. No paroxysmal pattern was found in the records, and no convulsive phenomena were observed.

*Biochemical studies.*—Urine chromatography was performed on specimens from 6 of our patients and 43 non-hospitalized normal controls. The studies were carried out by Dr. H. Eldon Sutton of the University of Michigan Medical School. No significant difference was observed between patients and controls. No abnormal spots were noted. Starch gel electrophoresis of the serum proteins were performed on specimens from 7 of the patients and 7 normal controls. The electrophoresis was carried out by Dr. Oliver Smithies of the University of Toronto. No major differences between the electrophoretic patterns of patients and controls have thus far been observed. Starch gel electrophoresis of spinal fluid proteins on 5 patients are still in progress.

*Course and prognosis.*—The course of illness in these patients is slow but steadily progressive. Many patients were not examined until they had reached an advanced stage of illness. The failure of many patients to present themselves earlier was probably due to the insidious onset, the

lack of pain or other discomfort, the lack of awareness of the illness by the patient, and the realization by most of the elders in the population that no treatment was available. Often the duration, as stated by the family, was very short in spite of advanced disease, and independent reliable sources of information often revealed that the patient had been affected many months or even a year or two earlier than the family would admit. Even considering these factors, the clinical course appears much shorter than that of Parkinson's disease seen in the U.S. which begins on the average at about 59 years of age and has a mean duration of about eight years (Kurland, 1958). Three patients with classical Parkinsonism have been recently found on Guam, all of whom have a considerably longer duration than the patients with dementia. However, the longest course among the 23 deceased cases in our present series was approximately six years (Case 24). The majority died within four to five years after symptoms appeared or within two to three years after the first clinical diagnosis of neurological disorder was established. All of the patients who were listed as cases of cortico-strial disease, cerebral pallidal degeneration and Parkinsonism by Mulder, *et al.*, in 1953 died sometime prior to September, 1959, which may be another indication of the short course of this disorder. The patients are completely incapacitated and bedridden in a relatively short time and they ultimately die with hypostatic pneumonia or in a state of cachexia due to poor food intake. Treatment has always been symptomatic, and the usual antispasmodic synthetic antihistamines or solanaceous preparations for Parkinson's disease show little or no beneficial effect since the patients have only mild tremor or rigidity.

## Discussion

Parkinson's disease, which is estimated will ultimately affect 2·4 per cent of the present population of the U.S. (Kurland, 1958) is one of the most common of the neurological disorders. ALS is also not an uncommon disease in the U.S. where 1 in 1,000 of the population can be expected ultimately to be affected (Kurland, 1956). However, presenile dementia (Alzheimer and Pick's disease) and Creutzfeldt and Jakob's disease are comparatively rare ailments despite the frequent reference to these disorders in the medical literature. No definite ætiological explanation or mode of pathogenesis is known for these latter diseases and they are customarily classified among the so-called degenerative disorders of the nervous system.

An overall summary of the clinical features presented by the patients in this paper is best expressed as a combination of Parkinson's disease and "presenile" dementia. In addition, during the course of illness, upper or upper and lower motor neurone signs developed in more than one-third of the cases. None of the cases described here can be considered as typical Parkinson's disease, senile dementia or ALS.

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The phenomenal prevalence of this unusual syndrome among the small native Chamorro population is recognized as a most serious problem on the Island (Mulder and Kurland, 1954, and Pieper and Fields, 1959). About 10 per cent of the deaths in the Chamorro adults in the past several years have been due to ALS. In 1959 and 1960, there were 19 deaths from Parkinsonism-dementia complex; this represents about 7 per cent of the deaths in the population 20 years and over.

The high prevalence of ALS and Parkinsonism with dementia on Guam raises the question of whether the association between these disorders is on a purely fortuitous basis. Although the matter cannot be conclusively settled at this time we shall show in subsequent publications that available evidence suggests that these syndromes, as they occur among the Chamorros, are clinical variants of a single entity presumably due to the same ætiologic mechanism.

Post-encephalitic disease must also be considered in the ætiology of these cases. An epidemic of Japanese B encephalitis occurred on Guam between December 1947 and April 1948 (Mulder, Kurland and Iriarte, 1954; Hammon, Tigertt and Sather, 1958; Edgren, Palladino and Arnold, 1958). However, in none of our 47 patients could an adequate history suggestive of clinical encephalitis preceding the onset of the cases be evoked from the family or the village nurse. We recognize that this differs from the report by Mulder, Kurland and Iriarte (1954) that one of their cases had been ill during the Japanese B encephalitis epidemic, and their impression that most of the others in their series presented symptoms and findings compatible with a post-encephalitic type of Parkinsonism. Although a clear decision on this matter must await the results of further serological and virus isolation procedures which are now under way, a limited study in 1954 failed to show any difference in antibody titres in controls and in the patients with the chronic neurological disorders so prevalent on Guam. Although the earliest date of Japanese B encephalitis on Guam is uncertain, the history of many cases of Parkinsonism with dementia pre-dates the first recognized epidemic in 1947–8. Also, dementia with Parkinsonism is not ordinarily described as a sequel of the B encephalitis cases which occur in Japan and other areas of the Western Pacific. Furthermore, all our patients would have been adults at the time of the epidemic in 1947–8, while clinical encephalitis on Guam had its highest incidence in the younger age groups, and especially young children. Pieper and Kurland (1958) reported that among 23 of the 25 survivors of the Japanese B encephalitis outbreaks who were hospitalized in 1947–8, none had developed evidence of Parkinsonism by 1957. As previously stated, the precise time of onset of the dementia and Parkinsonism is hard to determine because of the insidious appearance of the illness; but there was no pattern or temporal concentration for our 47 cases. For very

recent years at least there has been no indication of any annual fluctuation in the incidence of Parkinsonism with dementia on Guam.

There have been clinico-pathological case reports on subacute inclusion encephalitis which occurs with a gradual onset of illness without fever and an ingravescent course (Haymaker, *et al.*, 1958, and Malamud, *et al.*, 1950). However, at the present stage of investigation, there is no real clinical evidence that any of our 47 patients was a post-infectious case. Neither was there clinical or pathological severe generalized arteriosclerosis in these patients. None of them has had syphilis, by history or serology, and we found no evidence of intoxication by carbon monoxide or manganese.

The syndrome of Jakob (1921) and Creutzfeldt (1920) cortico-striatospinal degeneration as analysed by Wilson (1940) includes clinical features of mental deterioration, extrapyramidal signs and ALS. Our cases appear to resemble that syndrome. However, the clinical pattern of the Jakob-Creutzfeldt syndrome is rather ambiguous, for there appear to be almost as many varieties as the number of clinical series which have been reported. It is difficult to make an exact comparison of the syndrome in our series with the 20 or so sporadic cases which have been described (Wilson, 1940; Jervis, Hurdom and O'Neill, 1942; Bornstein and Jervis, 1955; Schwarz and Barrows, 1958). Some of the cases which have been reported do not demonstrate all of the three cardinal features which are usually associated with the Jakob-Creutzfeldt disorder. In addition, sensory disturbances were reported in the cases of Jansen and Monrad-Krohn (1938), Davison and Rabiner (1940) and others. Recently, Fisher (1960) reviewed the literature and presented 9 cases in which he described the clinical characteristics of Creutzfeldt-Jakob disease as organic dementia, hallucinations, cerebellar ataxia, unusual motor disease without amyotrophy, myoclonus and rigidity. His patients had a rapidly progressive illness, with stupor and coma; death occurred in two to six months after onset.

Except for a few familial cases, such as those of Worster-Drought, Hill, and McMenemey (1933), Davison and Rabiner (1940) and Jakob, Pyrkosch and Strube (1950), most of the previous studies describe one or a few sporadic cases with varying clinical features. Although our cases fit into a general pattern the variations which occur are relatively minor and can be readily recognized in the aggregate. However, the observer who reports a brief series of sporadic cases, may surmise, for a similar degree of variation, that he is dealing with a number of distinct symptom-complexes. On the other hand, another observer may assume that the wide variations described for Jakob-Creutzfeldt disease enables him to group together several clinical variants as having a common character with a common ætiologic basis. The clarification of the question regarding the unity or diversity of other forms of the Jakob-Creutzfeldt



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symptom complex will probably have to await biochemical elucidation of at least one of the major component members of this syndrome. In the meantime, comparative neuropathology such as described in the companion paper in this series, can be looked for to provide some leads in this direction.

The similarity of ALS and Parkinsonism-dementia complex among the Chamorros in terms of mean age of onset, sex ratio, the progression and duration of illness, the high incidence and geographic distribution, the familial patterns and the frequent presence of both disorders in the same patients suggests that they are variants of a single disease process over a fairly broad clinical spectrum. Further epidemiologic, genetic, clinical and pathologic studies on Guam can be expected to clarify not only this unusual and perhaps distinct disorder among the Chamorros, but also the cause and pathogenesis of ALS, some dementias and extrapyramidal diseases among other populations of the world.

## Summary

A clinical study has been made of 47 cases of a neurological disorder manifested by Parkinsonian syndrome with mental deterioration found among the indigenous (Chamorro) population of Guam. It exclusively affects Chamorro adults mostly in the fifth and sixth decades, and death usually results about three to five years after the recognized onset. This syndrome is responsible for about 7 per cent of the deaths among the adult Chamorro population. The onset is insidious and the main clinical features are mental deterioration of the organic type (dementia), the Parkinsonian syndrome, and evidence of motor neurone involvement. Almost all patients show hyperreflexia; over one-third showed evidence of upper motor neurone involvement and in 9 of the patients the ALS syndrome was also noted. At least 15 of the cases have had a family history of ALS, "Parkinsonism," or both.

Analysis and discussion of this disorder is attempted. It is felt that, although the disease may demonstrate the cardinal features of mental deterioration, extrapyramidal disease and motor neurone disease of the Jakob-Creutzfeldt syndrome, it cannot at present be considered as analogous to any one of the numerous clinical variants included in that grouping. There are also indications that this disorder on Guam is not a post-encephalitic state. Pathological and other studies now under way are expected to clarify these matters.

## Acknowledgment

The authors are grateful to Jose M. Torres of Merizo, Guam, an assistant in the Guam Neurological Research Center, NINDB, NIH, for his invaluable help. Dr. Robert Schwab, Massachusetts General Hospital, provided many helpful suggestions in the evaluation of case reports and

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EEGs. This report could not have been written without the records and clinical data written by Dr. S. Pieper. We wish to thank the public health nurses and village commissioners of Guam for their co-operation. EEGs were taken at the U.S. Naval Hospital 926.

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# PARKINSONISM-DEMENTIA COMPLEX, AN ENDEMIC DISEASE ON THE ISLAND OF GUAM

## II.—PATHOLOGICAL FEATURES

BY

ASAO HIRANO[1], NATHAN MALAMUD[2] AND LEONARD T. KURLAND[3]

### INTRODUCTION

IN the course of the investigations of the phenomenal incidence of amyotrophic lateral sclerosis on the Western Pacific Island of Guam, numerous patients with a syndrome of presenile dementia, features of Parkinsonism and, often, motor neurone involvement, have been observed. This syndrome, found exclusively in the indigenous Chamorro population, usually develops insidiously in the fifth to seventh decades and has an average duration of about four years from the onset of symptoms until death. This syndrome accounts for about 7 per cent of deaths among adult Chamorros. The possible relationship of this disorder to the amyotrophic lateral sclerosis of the Chamorros has been discussed by Hirano, Kurland, Krooth and Lessell in a companion paper in this series.

The neuropathological characteristics of the cases to be described were first observed by one of us (N. M.) in the course of examinations of specimens from Guam a few years ago. Stimulated by these findings, a concerted effort was made by one of the authors (A. H.) to obtain autopsies on all Guamanians dying of neurological disease. During a ten-month period, from August 1959 to June 1960, 11 of the 17 cases of Parkinsonism with presenile dementia reported here were autopsied.

There has been no report on the neuropathology of this disease as it occurs on Guam. The main purpose of this paper is to present the pertinent neuropathological features of the 17 necropsied cases. These are summarized in Tables I to III. Detailed reports are given for 2 cases and brief, additional remarks are made on the other 15 cases.

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TABLE I.—CLINICAL DATA ON PARKINSONISM-DEMENTIA COMPLEX AMONG THE CHAMORROS ON GUAM

| *Case No.* | *Sex* | *Year of onset* | *Date of death* | *Age at death* | *Approximate duration in years* | *Evidence of amyotrophic lateral sclerosis* | *Additional clinical diagnosis* |
|---|---|---|---|---|---|---|---|
| 1 | M | 1954 | Nov. 12, 1959 | 61 | 5 | 0 | |
| 2 | M | 1953 | Nov. 18, 1959 | 59 | 6 | 0 | Left eye was enucleated because of trauma |
| 3 | M | 1954 | Dec. 14, 1958 | 51 | 4 | 0 | Pulmonary tuberculosis |
| 4 | F | 1957 | Oct. 5, 1959 | 53 | 2 | 0 | |
| 5 | M | 1957 | Sept. 11, 1959 | 58 | 2 | 0 | |
| 6 | M | 1954 | July 23, 1959 | 59 | 5 | 0 | Hypertension |
| 7 | M | 1958* | Sept. 4, 1959 | 59 | — | 0 | Hypertension |
| 8 | M | 1955 | Oct. 11, 1959 | 68 | 4 | 0 | |
| 9 | M | 1956* | Dec. 26, 1957 | 52 | — | 0 | |
| 10 | M | 1953 | Mar. 9, 1958 | 63 | 5 | 0 | |
| 11 | M | 1956 | June 26, 1958 | 52 | 2 | + | Rheumatic heart disease |
| 12 | M | 1955 | Feb. 16, 1958 | 52 | 3 | + | |
| 13 | F | 1958 | April 30, 1960 | 48 | 2 | + | |
| 14 | M | 1959* | May 9, 1960 | 50 | — | 0 | |
| 15 | M | 1956 | May 11, 1960 | 59 | 4 | + | Diabetes mellitus Pulmonary tuberculosis |
| 16 | M | 1959* | May 24, 1960 | 53 | — | 0 | |
| 17 | M | 1954 | June 25, 1960 | 54 | 6 | + | |

*Diagnosis was first made on this date. The date of actual onset was not available in these cases.

## CASE REPORTS

*Case* 1.—A Chamorro man gave a history of progressive physical slowness and mental deterioration dating back to 1954 when, at the age of 56 years, he was retired from his government job. These clinical features were noted during hospitalizations at the Guam Memorial Hospital for phlebitis of the right leg in June 1956, and for gastrointestinal symptoms in March 1957. The patient was first seen at the Guam Neurological Research Center on July 14, 1957. At that time, he complained of forgetfulness and of being unable to recognize friends whom he had not seen recently. Memory for both recent and past events was poor. He was vaguely oriented as to time and place, and his recall of general information was poor. He walked leaning forward without moving his arms. His face was mask-like. There was generalized weakness, but no obvious muscle atrophy. There was plastic rigidity with cogwheel resistance of the extremities, and marked slowness when changing his posture or position. No tremor was noted. Muscle stretch reflexes were hyperactive and equal bilaterally, and no definite pathological reflexes were elicited. The cranial nerves were intact, and the sensory examination was normal. His illness, diagnosed as Parkinsonism with mental deterioration, progressed gradually. Extensive laboratory studies including blood serology, chemistry, hæmatology, urinalysis and radiological investigations were within

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normal limits. There was no family history of amyotrophic lateral sclerosis or Parkinsonism.

On examination in his home on September 16, 1959, he was emaciated and chair-ridden. He was completely silent, somewhat confused and apathetic throughout the examination, and it was almost impossible to communicate with him even in his native language. He seemed unable to comprehend or to follow simple commands during the examination. His mouth was tightly shut, so that his family had difficulty in feeding him. His jaw-jerk was hyperactive, and a snout reflex was present. Eye movements and pupillary responses were normal. There was marked rigidity, but no tremor in the extremities. Muscle stretch reflexes were hyperactive and equal bilaterally; there was still no Babinski sign. Focal muscular atrophy and fasciculations were absent.

When he was observed again on October 5, 1959, he was bedridden, and it was almost impossible to open his mouth to feed him. He deteriorated rapidly and expired on November 12, 1959.

*Post-mortem examination.*—The general autopsy showed bilateral hypostatic pneumonia and infected decubiti over the sacral area.

*Macroscopic observations.*—The unfixed brain weighed 1,064 grammes. The total protein of cerebrospinal fluid taken from the cisterna magna at the time of autopsy was 39 mg. per cent. The dura mater and superior longitudinal sinus were intact. The cerebral hemispheres were well developed, symmetrical and covered by slightly milky and thickened leptomeninges. The cerebral gyri were narrowed and the sulci were widened in the fronto-temporal areas (fig. 1A, Plate LXXXIII). The blood vessels at the base of the brain formed a complete circle of Willis. Both posterior cerebral arteries arose from the internal carotid arteries. The right anterior cerebral artery was very small between the internal carotid and anterior communicating arteries. In contrast, the left anterior cerebral artery was very large, and it supplied the anterior communicating artery and major distal portion of the anterior cerebral arteries bilaterally. The walls of the major arteries were thin and elastic and contained few atheromatous plaques. The cranial nerves appeared normal. Coronal sections of the hemispheres revealed well-demarcated grey and white matter. The cortex in the frontal and temporal lobes appeared to be narrowed. The ventricular system was symmetrically dilated (fig. 1B). There was gross atrophy of the globus pallidus bilaterally. The Sylvian fissure was widened due to atrophy of the frontal and temporal gyri, as well as the insula. The substantia nigra lacked its normal dark appearance (fig. 1C). The locus cæruleus was not identified; otherwise, transverse sections of the cerebellum and brain-stem were unremarkable.

*Microscopic observations.*—The cerebral cortex was covered by slightly thickened and fibrotic leptomeninges without acute inflammatory changes.

The cortical architecture was relatively well preserved in most areas with the exception of the temporal cortex which presented disorganization of its laminar arrangement. Scattered throughout the frontal and temporal cortex were large numbers of ganglion cells which showed alterations. There was loss of Nissl substance in some of the neurones and accumulation of intracytoplasmic lipid granules in others. The most prominent features were abundant neurofibrillary changes (fig. 2A) and intracytoplasmic granulovacuolar bodies (fig. 2B). There were only occasional neuronophages, satellitosis and actual disapppearance of ganglion cells. These changes were most severe in the temporal lobe, particularly in Sommer's sector and the presubiculum of the hippocampal gyrus. The frontal pole, orbital gyri and cingulate gyrus were somewhat more involved than other parts of the frontal lobe. The ganglion cells of the parietal and occipital lobes were much less affected, and the visual cortex was entirely free of neurofibrillary changes and granulovacuolar bodies. There was severe astrocytic gliosis in

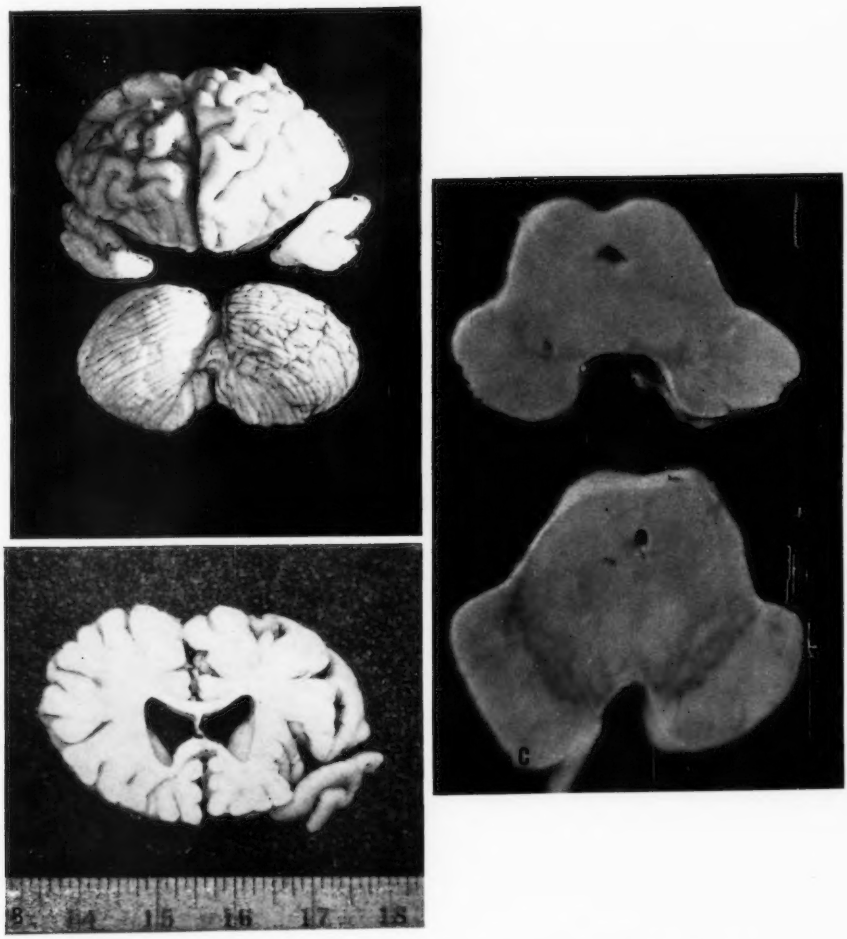

FIG. 1 (*Case* 1).—Parkinsonism-dementia complex on Guam. A, Atrophy of frontal lobes. Cerebellar hemispheres are normal. B, Moderate dilatation of frontal horns. C, Loss of pigment in substantia nigra in upper figure as compared with the normal in the lower.

*To illustrate article by Asao Hirano, Nathan Malamud and Leonard T. Kurland.*

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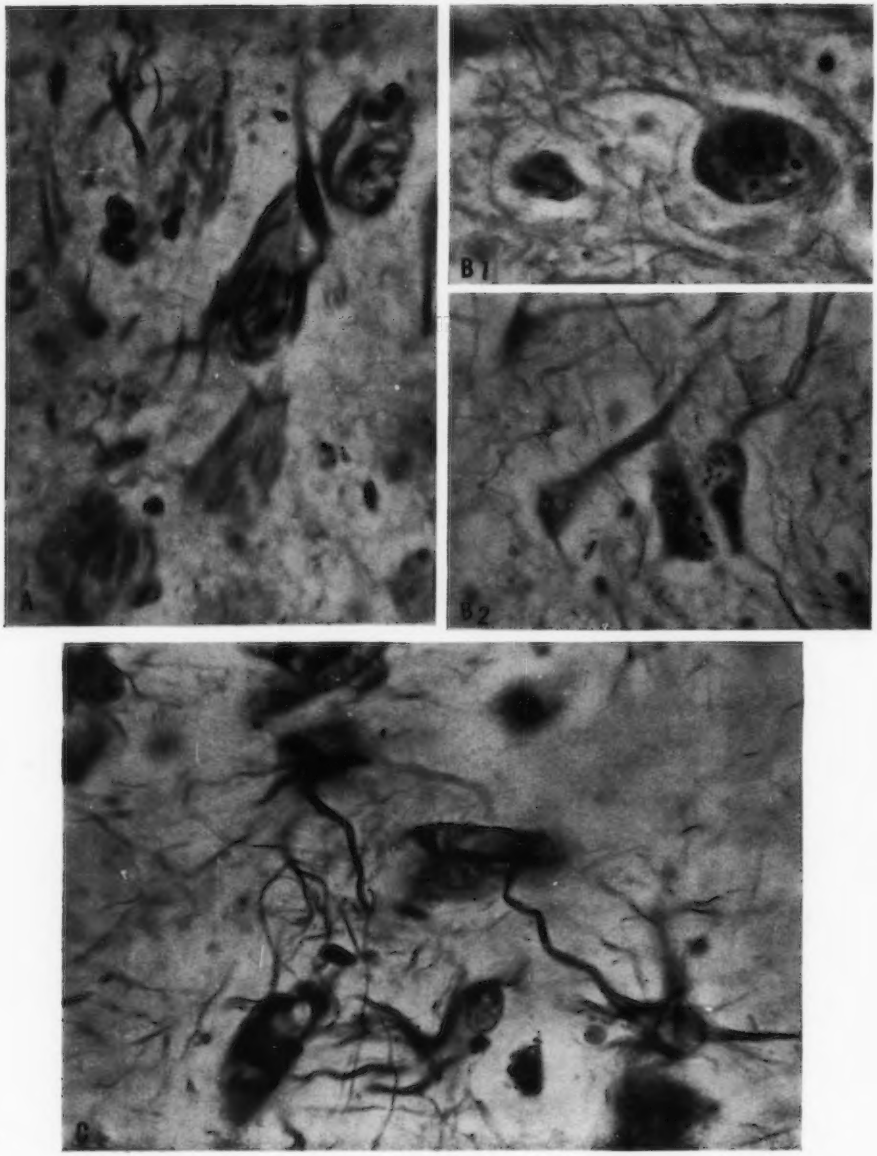


FIG. 2 (*Case* 1).—Sommer's sector. A, Neurofibrillary change. ×970. B, Nerve cell with granulovacuolar bodies. ×970. (A–B: Bielschowsky stain.) C, Hypertrophic astrocytes. ×970. (von Braunmühl stain.)

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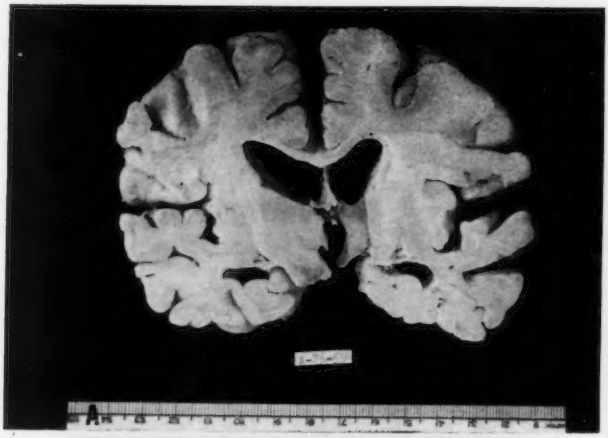

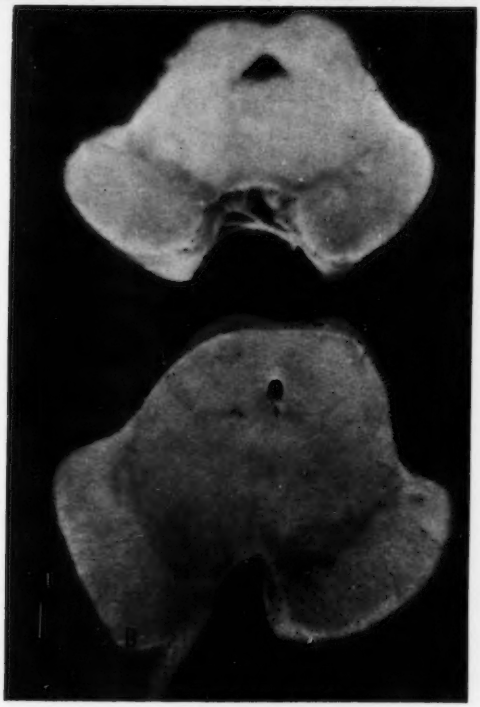

FIG. 3 (*Case* 2).—A, Mild general atrophy and moderate dilatation of lateral ventricles. A small block of tissue was removed along the third ventricle on right side. B, Loss of pigment in substantia nigra in upper figure as compared with the normal in the lower.

*To illustrate article by Asao Hirano, Nathan Malamud and Leonard T. Kurland.*

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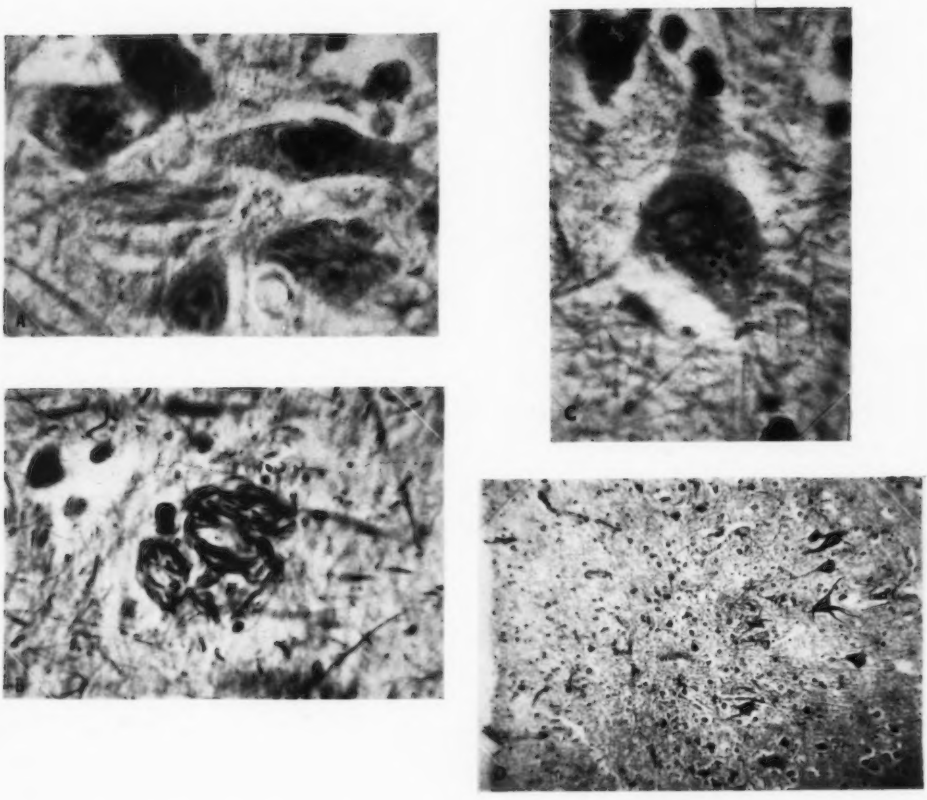

FIG. 4 (*Case* 2).—Sommer's sector. A, Argyrophilic Alzheimer's neurofibrillary changes of nerve cells. ×1,100. B, Typical condensation of argyrophilic neurofibrils of a pyramidal cell. ×1,500. C, Granules in cytoplasm of a pyramidal cell are argyrophilic and surrounded by vacuoles. ×1,400. D, Subiculum. Nerve cells with typical Alzheimer's neurofibrillary changes. ×150. (A–D: von Braunmühl stain.)

*To illustrate article by Asao Hirano, Nathan Malamud and Leonard T. Kurland.*

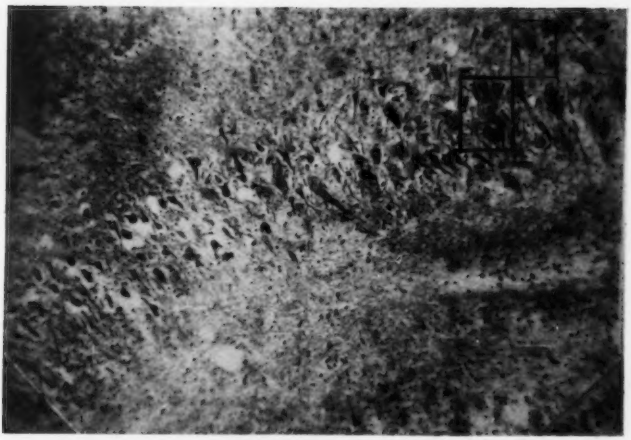

FIG. 5 (*Case* 3).—Sommer's sector. A, Altered pyramidal cells with typical Alzheimer's neurofibrillary change. ×110. B, Higher magnification of the area illustrated in A (square). ×900. C, Higher magnification of the area illustrated in A (thickly-lined square). ×1,070. (A–C: Bielschowsky stain.)

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FIG. 6 (*Case* 3).—Sommer's sector. A and B, A mass of comparatively weakly argyrophilic neurofibrils. Adjacent neuraxons are thickened and strongly argyrophilic. ×1,300. C, Presubiculum. A pyramidal cell with typical Alzheimer's neurofibrillary change. ×1,150. D, Subiculum. ×500. (A–D: Bielschowsky stain.)

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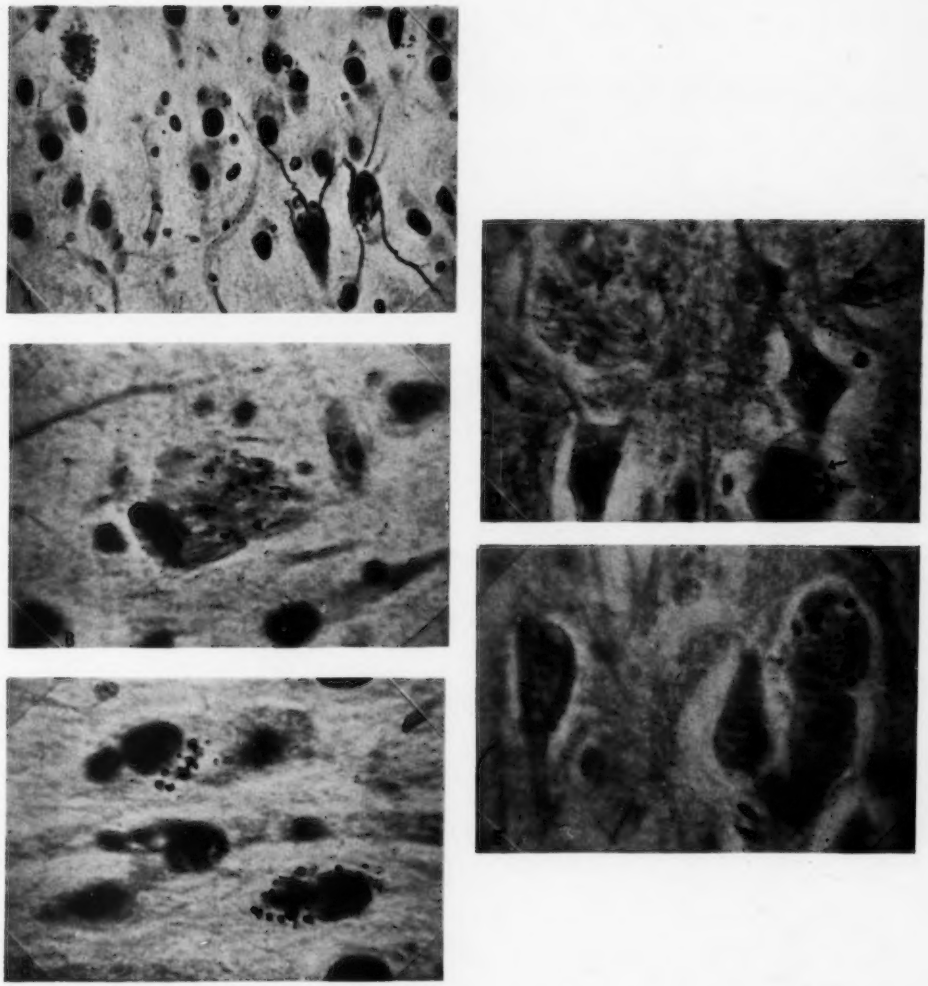

FIG. 7 (*Case* 4).—Sommer's sector. A, Two pyramidal cells with typical Alzheimer's neurofibrillary changes at the lower right corner. A pyramidal cell with a large amount of argyrophilic granular substance in its cytoplasm at the upper left corner. ×490. B, An enormously swollen pyramidal cell with a combination of Alzheimer's neurofibrillary change and granulovacuolar bodies. ×1,100. C, Two pyramidal cells with granulovacuolar bodies. Tiny argyrophilic granules surrounded by vacuoles are present in cytoplasm. ×1,100. D, An atypical plaque with neurofibrillary change and a pyramidal cell with granulovacuolar bodies (arrows). ×1,070. E, Pyramidal cell with typical Alzheimer's neurofibrillary change and another with typical granulovacuolar bodies. ×1,070. (A–E: von Braunmühl stain.)

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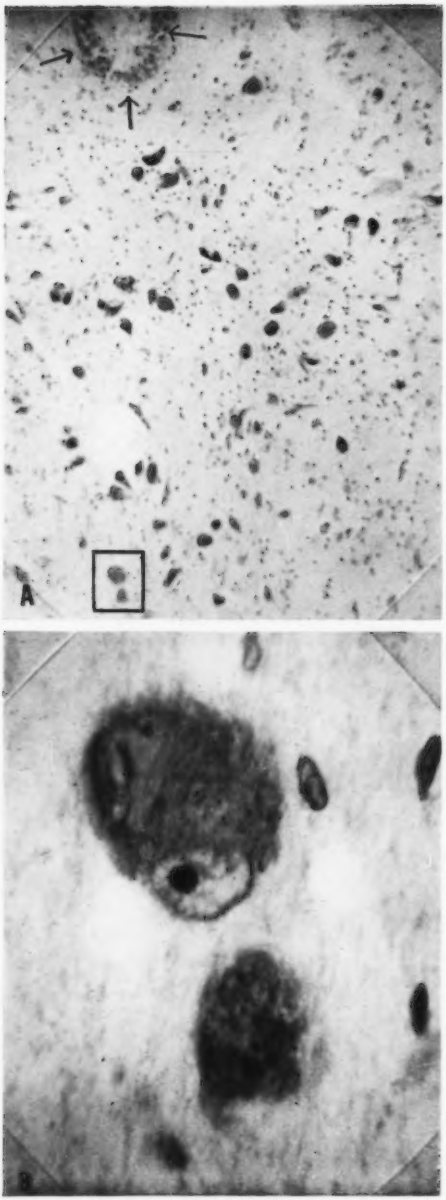


FIG. 8 (*Case* 8).—Nucleus dorsalis raphes at cranial pons. A, A series of various changes of nerve cells. Arrows mark off ependymal lining cells. ×110. B, Higher magnification of the area illustrated in A (square). Swollen cytoplasm of a nerve cell with eccentric nucleus is filled with thickened neurofibrils and a few deep-green pigmentary granules. ×980. (A–B: Toluidine blue stain.)

*To illustrate article by Asao Hirano, Nathan Malamud and Leonard T. Kurland.*

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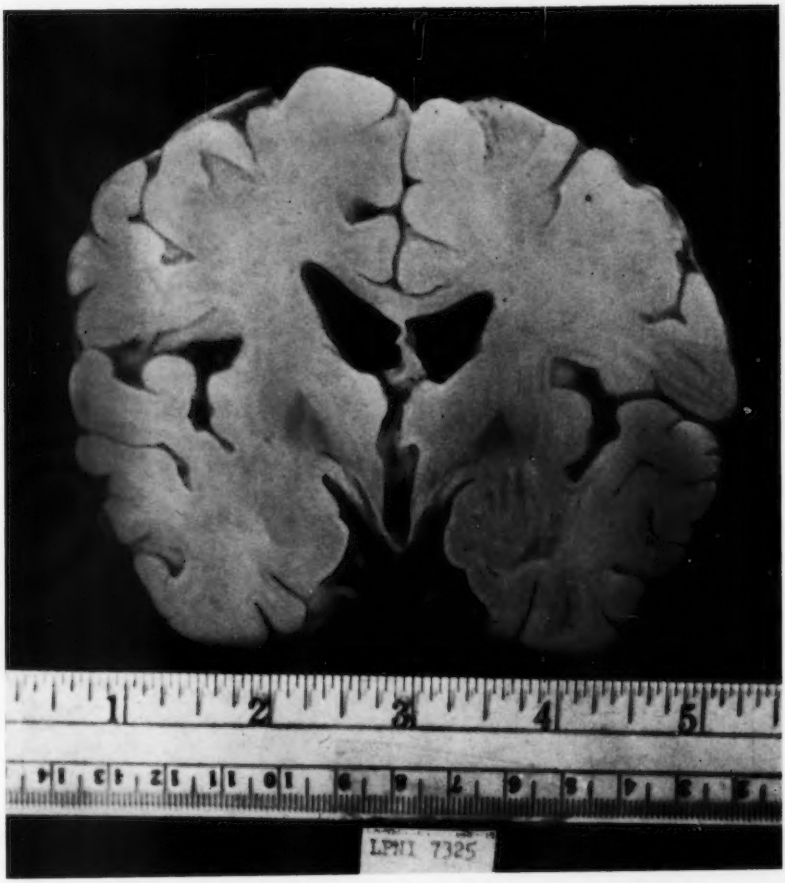


FIG. 9 (*Case* 9).—Symmetrical atrophy and brown pigmentation of the globus pallidus.

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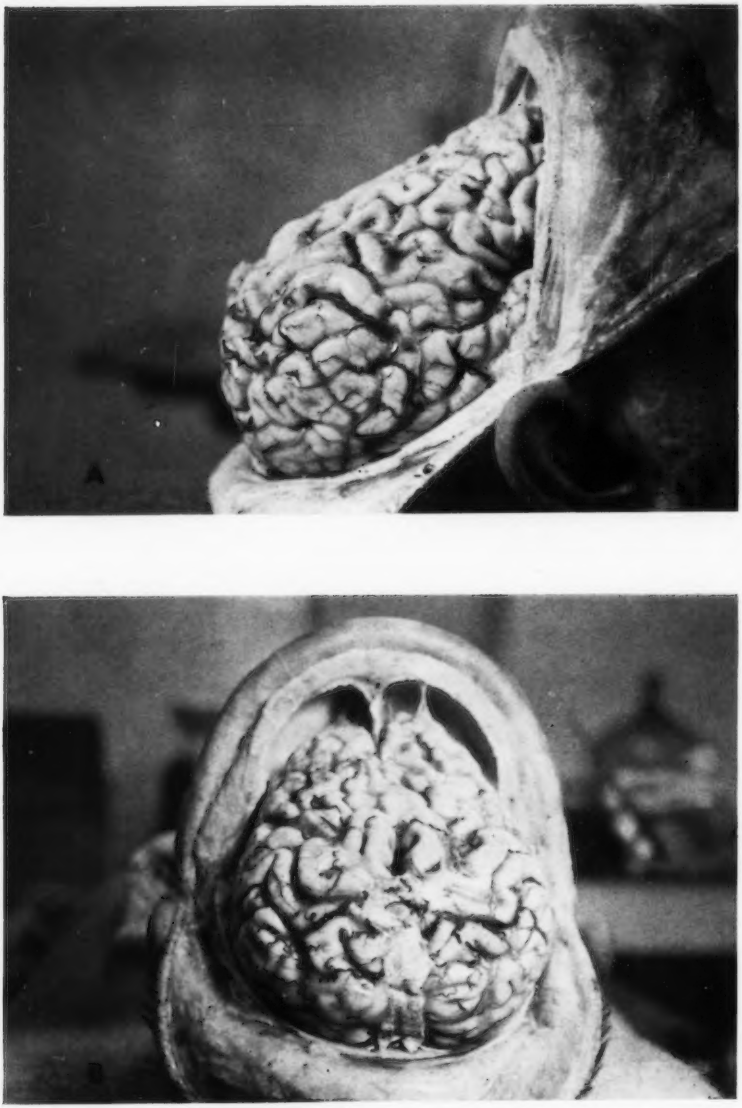

FIG. 10 (*Case* 13).—A–B, Autopsy specimen showing disproportionate size of skull to brain, especially frontal and temporal areas.

*To illustrate article by Asao Hirano, Nathan Malamud and Leonard T. Kurland.*

FIG. 11 (*Case* 13).—A, Moderate dilatation of both frontal and temporal horns. B, Depigmentation of substantia nigra.

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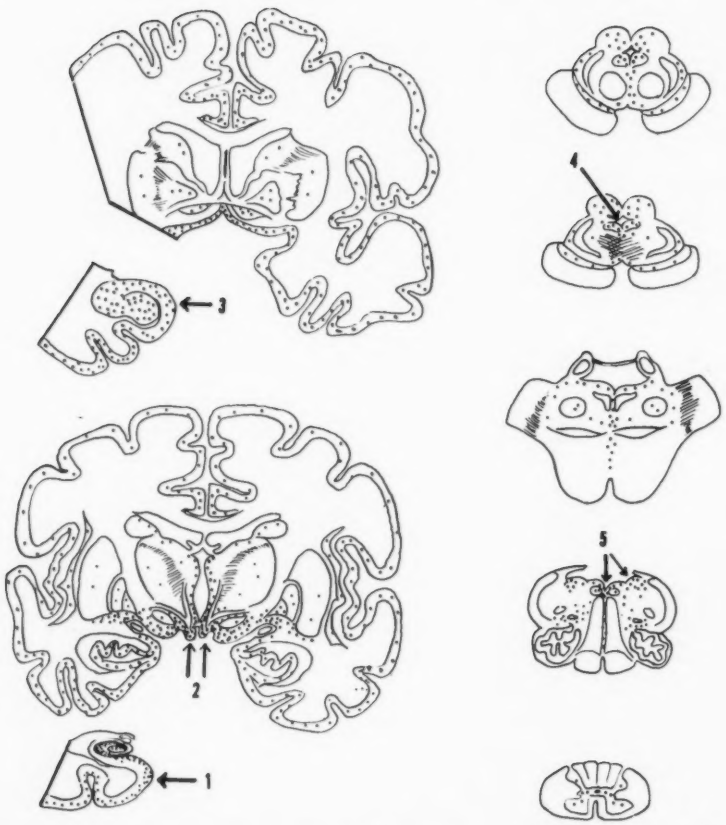


FIG. 12.—Drawing of distribution of Alzheimer's neurofibrillary changes in Parkinsonism-dementia complex on Guam. The most severely involved areas are: (1) Sommer's sector and subiculum. (2) Hypothalamus and adjacent nuclei, including cranio-medial portion of substantia nigra. (3) Amygdaloid nucleus and adjacent temporal cortex. (4) Periaqueductal area. (5) Dorsal motor nucleus of vagus, midline raphe and reticular nuclei.

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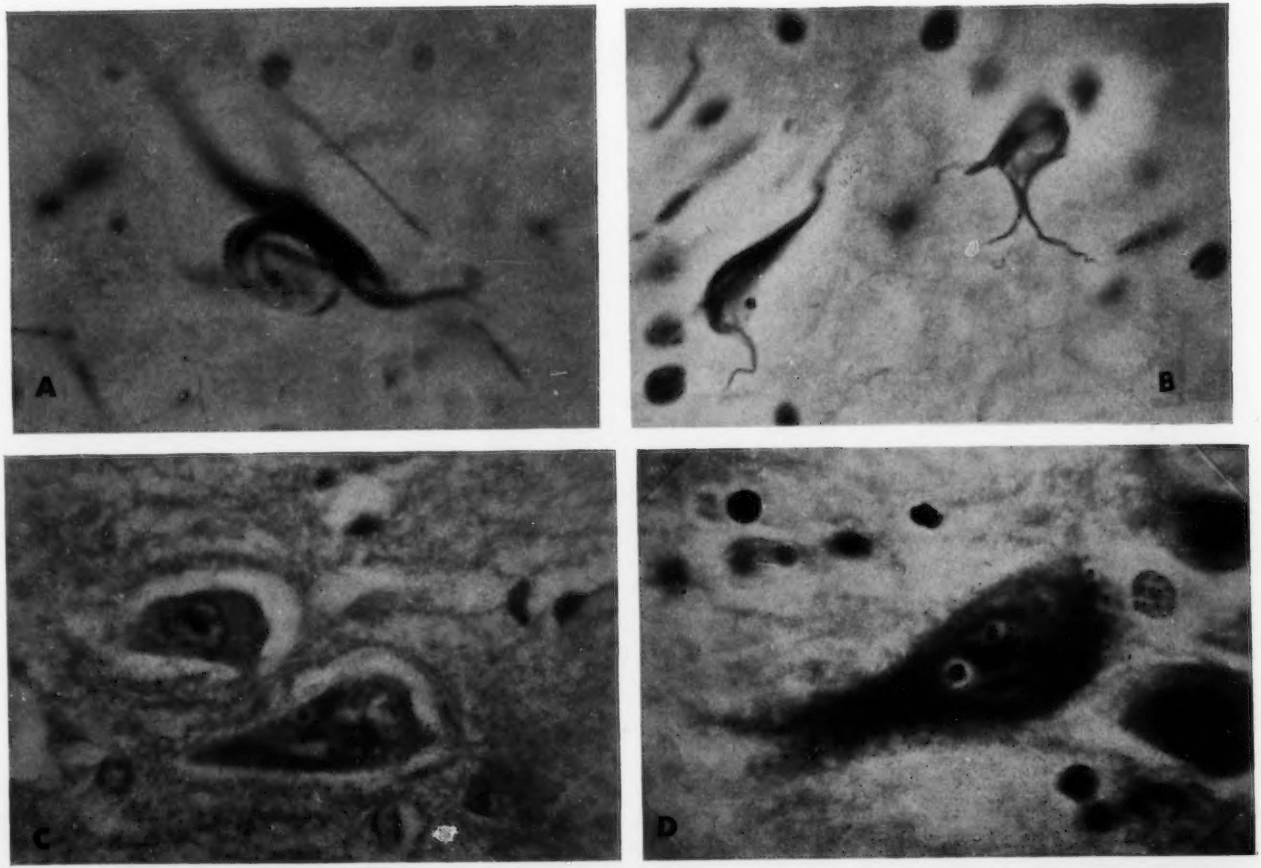


FIG. 13.—Parkinsonism dementia complex on Guam. Typical Alzheimer's neurofibrillary change in ganglion cells of cerebral cortex. ×970. Granulovacuolar bodies evident in C and D. (A–B: von Braunmühl stain; C–D: Hæmatoxylin-eosin stain.)

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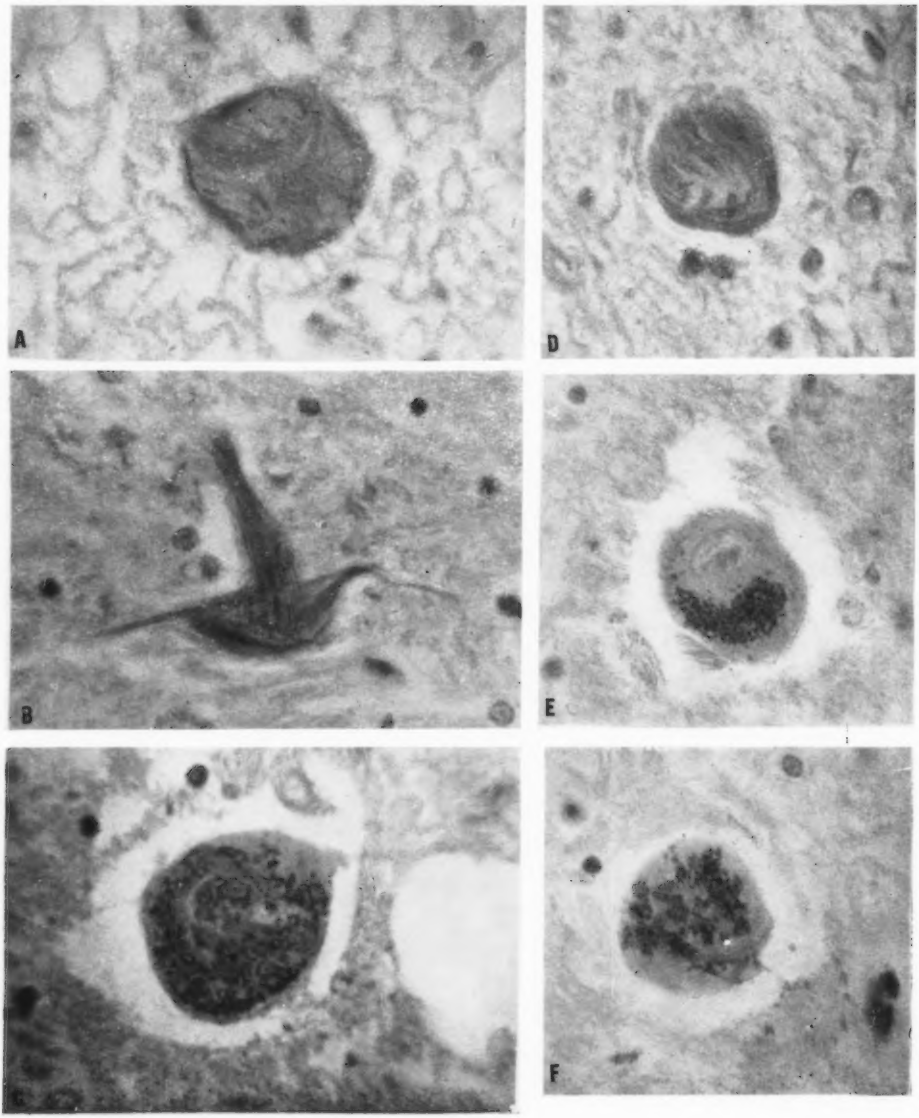


FIG. 14.—Parkinsonism-dementia complex on Guam. Typical Alzheimer's neurofibrillary change in pigmented cells of substantia nigra and brain-stem. ×970. (Hæmatoxylin-eosin stain.)

*To illustrate article by Asao Hirano, Nathan Malamud and Leonard T. Kurland.*

the involved cortex, as well as in the adjacent white matter (fig. 2c). Macrophages were scant and only scattered sudanophilic granules were found free in the cerebral tissue. Reactive microgliosis was commonly observed. Senile plaques were not observed.

The neurofibrillary changes were located primarily in the hypothalamus, amygdaloid nucleus and substantia nigra, and were relatively rare in the basal ganglia and thalamus. Subependymal gliosis was prominent along the third and lateral ventricles. A poverty of ganglion cells in the globus pallidus was associated with severe gliosis. The pigmented zone of the substantia nigra showed severe neuronal loss with scattered neurofibrillary changes in the remaining cells of the medial and cranial portions of this structure. The caudal portion of the substantia nigra showed severe astrocytic gliosis, so extensive that almost its entire structure was replaced by a glial fibrous network. A Sudan stain of this region showed little sudanophilic material. There were no Lewy bodies. The tegmentum of the mid-brain and the periaqueductal area also contained scattered neurofibrillary changes.

In the pons and medulla there was severe cell loss in the locus cæruleus and the dorsal nucleus of the vagus. There were occasional neurofibrillary changes in the cells of the reticular formation, but none in the pontile or inferior olivary nuclei. In the latter, the neurones were filled with lipofuscin. The cerebellum was free of any abnormality. The dentate nucleus contained an excessive accumulation of lipofuscin. In the spinal cord occasional neurofibrillary changes were noted in the small cells of the lateral horn at the cervical and thoracic levels.

There was no evidence of demyelination or inflammatory changes.

*Case* 2.—At the age of 53 years, this Chamorro farmer developed early signs and symptoms of dementia and a Parkinsonian syndrome with no known antecedent febrile illness. On examination a characteristic Parkinsonian posture and gait were evident. There was a tremor of the hands, but neither the generalized increase in muscle tonus nor the cogwheel rigidity was pronounced. After six years of slowly progressive illness, the patient died of cachexia and hypostatic pneumonia. The patient's mother had died of amyotrophic lateral sclerosis.

*Post-mortem examination.*—The findings of the general autopsy were severe emaciation, decubiti of the buttocks and sacral area and hypostatic pneumonia.

*Macroscopic observations.*—The unfixed brain weighed 960 grammes. The major arteries at the base of the brain were thin and elastic, and free of atheromatous plaques. The left vertebral artery was three times larger than that of the right side. There was moderate atrophy of the cerebral cortex in the frontal and temporal lobes bilaterally. Coronal sections of the hemispheres revealed narrowing of the cortex, and moderate dilatation of the ventricular system (fig. 3A). There was bilateral gross atrophy of the globus pallidus. The brain-stem and cerebellum were unremarkable except for the lack of pigmentation of the substantia nigra (fig. 3B) and locus cæruleus bilaterally.

*Microscopic observations.*—There were severe alterations in the ganglion cells of the frontal and temporal lobes, especially in Sommer's sector and the temporal pole. Many of the neurones showed neurofibrillary changes of varying degree, and in some of the neurones there were also intracytoplasmic granulovacuolar bodies (fig. 4). There was hypertrophic astrocytic gliosis, but inflammatory changes were absent. Macrophages were not found. There were no senile plaques or Pick's globular argyrophilic inclusions observed. A severe degeneration of the globus pallidus was characterized by a paucity of neurones and reactive gliosis, the latter consisting predominantly of glial fibres. The change was bilateral and symmetrical, involving all parts of the pallidum, in contrast to the absence of changes in the adjacent putamen and caudate nuclei. There was equally severe, symmetrical degeneration of the substantia nigra with only scat-

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tered islands of pigment-containing neurones remaining, some of the pigment being stored in phagocytes or lying free in the tissue. There was dense reactive gliosis, composed largely of fibres. A more moderate degeneration affected the nuclei of the brain-stem bilaterally; primarily, those of the periaqueductal grey matter and the nucleus pigmentosus. Neurofibrillary changes, with or without accompanying degeneration, were present in the anterior perforating substance, various hypothalamic nuclei, amygdaloid nucleus, and in the tegmentum of the brain-stem, including the degenerated substantia nigra, nucleus pigmentosus, mid-line raphe and dorsal nucleus of the vagus. Neurofibrillary changes were not observed in the visual cortex, pontile nuclei, inferior olivary nucleus, Purkinje cells or dentate nucleus. There was no demyelination of the pyramids or the lateral columns, but a few macrophages containing sudanophilic material were scattered in the vicinity of blood vessels in these areas.

*Case* 3.—At 47 years of age, this Chamorro male developed symptoms of organic mental disease followed by Parkinsonism. When he died four years later, he was cachectic and had pulmonary tuberculosis. Neuropathological findings were essentially the same as those of the previous 2 cases. The abundant neurofibrillary changes found in this case are illustrated in figs. 5 and 6.

*Case* 4.—This Chamorro female developed symptoms at 51 years of age and died two years later. The outstanding pathological features were ganglion cell changes with abundant neurofibrillary alterations and intracytoplasmic granulovacuolar bodies; their distribution was similar to that of the previous cases. Fig. 7 shows these changes, together with an atypical plaque which was observed.

*Case* 5.—At the age of 56 years this man developed dementia and Parkinsonism. The total course of his illness was about two years. There was unusually severe involvement of the substantia nigra and brain-stem and neurofibrillary changes were present throughout the brain, including the usually-spared inferior olive, olfactory bulb and the motor neurones of the brain-stem. Another unusual feature in this case was the rare neurofibrillary changes in the visual cortex. Examination of the circle of Willis disclosed that the posterior communicating vessels were of the same calibre as the posterior cerebral arteries and appeared to arise from the internal carotid vessels. A small branch from each of the posterior cerebral arteries communicated with the basilar artery.

*Case* 6.—This male patient developed symptoms of Parkinsonism in 1954, but a clinical diagnosis was not made until May 1957. He was also demented and died at the age of 58 years in a state of cachexia on July 23, 1959. He was known to have hypertension (B.P. 190/120–210/140) since 1956. Microscopically, this case showed a particular abundance of cells with neurofibrillary changes; these were most prominent in the substantia nigra, the dorsal motor nucleus of the vagus and the hypothalamic nuclei. In addition, moderately severe athero- and arteriolo-sclerotic changes were evident in the cerebral vessels.

*Case* 7.—This male patient died at the age of 59 years with a progressive dementia and Parkinsonism picture of uncertain duration. He also had known hypertension which ranged from 166/110 to 210/140. General autopsy showed left ventricular hypertrophy and pulmonary congestion. However, the blood vessels at the base of the brain were almost free of atheromatous plaques. There were severe neuronal changes of the same nature as noted in the preceding cases.

*Case* 8.—This male patient died at 68 years of age; the duration of his illness was four years. Various changes of nerve cells in the nucleus dorsalis raphes at the cranial pons are illustrated in fig. 8. The Nissl stain demonstrates the swollen cytoplasm of a

nerve cell with an eccentric nucleus which is filled with altered neurofibrils and a few deep-green staining pigmentary granules. Small subacute infarcts were found in the ventral thalamus. Other neuropathological findings were similar to the cases described in detail.

*Case* 9.—The diagnosis of presenile dementia with Parkinsonism was made in 1956: he died the following year at the age of 52 years. Macroscopically, the most outstanding changes were the symmetrical atrophy and brown pigmentation of the entire globus pallidus (fig. 9) and the substantia nigra. Microscopically, the majority of neurones had disappeared or were absent in these structures; reactive gliosis and some pigment granules in phagocytes and glial cells were present. There were also large round bodies with granular deposits representing some unknown process of degeneration. In the oculomotor nuclei there was a paucity of cells, and of those remaining, some contained neurofibrillary tangles. In spite of this there were no discernible manifestations of ocular disturbance.

*Case* 10.—At 58 years of age, this man developed symptoms of a slowly progressive dementia with Parkinsonism and died five years later. In this case, neurones with neurofibrillary changes were most numerous in the nuclei of the hypothalamus, the peri-aqueductal region of the mid-brain, and to a lesser degree in the cerebral cortex.

The following two patients presented clinical features of amyotrophic lateral sclerosis, in addition to dementia and Parkinsonism. Details of the clinical aspects of these cases are included in the report by Hirano, Kurland, Krooth and Lessell.

*Case* 11.—This Chamorro man died at the age of 52 years after an illness of only two years. General post-mortem examination showed inactive mitral valvulitis of the heart and multiple decubiti. Neuropathological findings: the brain, which weighed 1,000 grammes after formalin fixation, was small and symmetrical and showed no abnormality other than suggestive atrophy of the frontal gyri. There was no evidence of atherosclerosis in the basal arteries. Coronal sections revealed atrophy of the globus pallidus and depigmentation of the substantia nigra. The significant microscopic changes were as follows: (*a*) Chronic bilateral degeneration, characterized by loss of neurones and replacement gliosis, which was most marked in the substantia nigra and locus cæruleus and more moderate in the globus pallidus and tegmental parts of the brain-stem. There were no Lewy bodies. (*b*) Degeneration of a severe degree in many areas of the cerebral cortex, characterized by depletion of neurones, active micro- and astroglial reactions, without senile plaques or signs of cerebral vascular disease. The Betz cell region of the cortex appeared to be the least affected. (*c*) Bilateral demyelination of the pyramidal tracts. (*d*) Bilateral degeneration of the hypoglossal nuclei and of the anterior horn cells in the spinal cord. (*e*) Neurofibrillary lesions similar to those described in the foregoing cases were numerous in the hypothalamus and tegmentum of the brain-stem, and moderately severe in the cerebral cortex and other areas.

*Case* 12.—A Chamorro man who died at the age of 52 years presented initially as an organic mental syndrome with Parkinsonian features, and subsequently developed additional motor neurone signs. On general post-mortem examination there was bilateral pulmonary congestion and œdema and chronic cystitis. The formalin-fixed brain weighed 940 grammes. It was small and symmetrical with a suggestion of atrophy of the frontal gyri. Blood vessels appeared normal. Coronal sections revealed moderately enlarged lateral ventricles, questionable diffuse cortical atrophy, and slight atrophy of the globus pallidus and substantia nigra. The spinal cord was

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thinner than normal throughout, and after sectioning, the anterior horns could not be identified. The anterior and lateral fascicles were reduced in size. Microscopically, two types of change were noted: (1) Degeneration of anterior horn cells, most marked in the cervical regions, together with demyelination of the pyramidal tracts and a paucity of Betz cells in the motor cortex. (2) Atrophy with diffuse cerebral changes, characterized by a disappearance of neurones, severe in the substantia nigra and globus pallidus and moderate in the cerebral cortex, hypothalamus and periaqueductal region. There were numerous neurones with neurofibrillary changes of Alzheimer scattered throughout the affected areas.

*Cases* 13 *to* 17.—The clinical and pathological features which are included in Tables I to III are essentially similar to those already presented. A brother of Case 14 had died of presenile dementia with Parkinsonism. A brother of Case 17 had died of "Lytico," the term commonly used by the Chamorro population to refer to amyotrophic lateral sclerosis, the Parkinsonian syndrome, or other progressive paralytic disease. In Case 15 the septum pellucidum was virtually absent, being represented only by rudimentary fibres, in the vicinity of the blood vessels. In this case there was no cerebral substance between the mammillary bodies and the adjacent area, the third ventricle opened widely into the basal cistern.

## Discussion

All 17 cases presented in this report have certain neuropathological changes in common. Macroscopically, there is cerebral atrophy, pallidal atrophy and loss of pigmentation in the substantia nigra and locus cæruleus. Microscopically, severe neuronal alterations associated with gliosis are observed in certain areas. The altered ganglion cells show two specific features: Alzheimer's neurofibrillary changes and intracytoplasmic granulovacuolar inclusion bodies. In addition, accumulation of intracytoplasmic lipid granules and other manifestations of nonspecific neuronal degeneration are observed. The loss of neurones is most apparent in the globus pallidus and the substantia nigra. Each of these features will be discussed in detail below:

(1) *Cerebral Atrophy*

All of the patients presented with a clinical history of progressive dementia which is described in greater detail in the clinical report (Hirano, Kurland, Krooth and Lessell). Although the skull is of normal size, the brain is usually small, and there is a compensatory increase in the quantity of cerebrospinal fluid (figs. 10A and B). The total protein content of this fluid is normal. The weight of the brain ranges from 860 to 1,310 grammes with a mean of 1,039 grammes (Table II). This is appreciably less than the mean weight of European brains which, for ages 51 to 60 years, average 1,338 grammes for males and 1,254 grammes for females (von Braunmühl, 1957). Although only a limited number of adult Chamorro brains in which neurological disease was absent have been examined, their weight falls within the normal range for Europeans.

The question of racial difference of the brain weight is further discounted because of the difference between the actual skull capacity and

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TABLE II.—PARKINSONISM–DEMENTIA COMPLEX ON GUAM (POST-MORTEM FINDINGS)

| *Case No.* | *Weight of brain (grammes)* | *Atheromatous plaques major arteries* | *Cerebral atrophy* | *Dilatation of ventricles* | *Pallidal atrophy* | *Pallor of substantia nigra* | *General pathological findings* |
|---|---|---|---|---|---|---|---|
| 1 | 1,064 | Minimal | Moderate | Moderate | + | + | Hypostatic pneumonia, infected decubiti |
| 2 | 960 | None | Moderate | Moderate | + | + | Hypostatic pneumonia, emaciation, decubiti |
| 3 | 946 | None | Moderate | Minimal | + | + | Pulmonary tuberculosis |
| 4 | 970 | Minimal | Moderate | Minimal | + | + | Pulmonary congestion |
| 5 | 1,120 | None | Minimal | Minimal | + | + | Examination was limited to the brain only |
| 6 | 960 | Severe | Moderate | Moderate | + | + | Examination was limited to the brain only |
| 7 | 980 | Minimal | Moderate | Minimal | + | + | Left ventricular hypertrophy, pulmonary congestion |
| 8 | 1,140 | None | Minimal | Minimal | + | + | Hypostatic pneumonia, eczematoid dermatitis |
| 9 | 1,115 | None | Moderate | Moderate | + | + | Sacral decubiti, pulmonary congestion and œdema |
| 10 | 1,310 | None | Minimal | Moderate | + | + | Nephrosclerosis, pulmonary congestion and œdema |
| 11 | 1,000 | None | Minimal | Minimal | + | + | Inactive mitral valvulitis, multiple decubiti |
| 12 | 940 | None | Minimal | Moderate | + | + | Pulmonary congestion and œdema, chronic cystitis |
| 13 | 860 | None | Moderate | Moderate | + | + | Hypostatic pneumonia |
| 14 | 1,100 | Minimal | Moderate | Moderate | + | + | Hypostatic pneumonia |
| 15 | 980 | None | Moderate | Moderate | + | + | Pulmonary tuberculosis |
| 16 | 1,110 | Moderate | Moderate | Moderate | + | + | Examination was limited to the brain only |
| 17 | 1,110 | None | Moderate | Moderate | + | + | Examination was limited to the brain and high cervical cord |

the volume of the brain at autopsy. Widening of the sulci and narrowing of the gyri are more apparent over the frontal and temporal lobes, whereas the parietal and occipital lobes are relatively well preserved. The cerebral atrophy is always bilateral, but the lobar atrophy characteristic of Pick's disease is not found. On coronal sections the only significant abnormality is minimal to moderate dilatation of the lateral ventricles, particularly in the frontal and temporal horns. However, it is important to note that sectioning the hemispheres in these cases may not show any striking gross abnormality of the cortex or white matter despite severe involvement histologically.

(2) *Depigmentation of the Substantia Nigra and Locus Cæruleus; Atrophy of the Globus Pallidus*

The substantia nigra lacks its normal black pigmentation, appears pale brown at all levels and seems atrophic bilaterally (figs. 11A and B). Identification of the locus cæruleus is usually impossible on gross examination due to the loss of its black pigmentation. The globus pallidus shows moderate to severe atrophy in all specimens.

(3) *Neurofibrillary Changes*

These are conspicuous in all cases. They are readily seen with axon stain preparations such as Bielschowsky's and von Braunmühl's. The mildly affected ganglion cells show well-preserved cellular elements such as nucleus, nucleolus, cellular dendrites and cytoplasm with the exception of a single or a few abnormally thickened argyrophilic neurofibrillary filaments in the periphery of the cytoplasm. Other cells contain coarse, thick fibres which coil around the nucleus a few times from the apical dendrite to the base. Still others form a mass of fine tangles of fibres which fills the entire cytoplasm. Generally speaking, this spool-like type stains less intensely than the thick "rope" type. The nucleus is usually deformed and peripherally located, so that the perikaryon assumes a more or less swollen, rounded form. Many of the severely affected ganglion cells are completely replaced by tangles of the fibrillary mass. Frequently, they appear like a torch of fibrils with no other cellular elements remaining, particularly so in the pyramidal cells of the hippocampus.

Malamud, Haymaker and Pinkerton (1950) observed that neurofibrillary changes can also be seen clearly with Nissl or hæmatoxylin-eosin stains of either frozen, paraffin or celloidin-embedded sections. Greenfield and Bosanquet (1953) also demonstrated the fibrils in cases of Parkinsonism with Lendrum's phloxin tartrazine stain, and observed that the fibrils which stained feebly with Congo red demonstrated anisotropism under polarized light.

Ishii (1958) studied the neurofibrillary changes in 10 brains of presenile and senile dementia. When Congo red stain was applied, some

TABLE III.—PARKINSONISM–DEMENTIA COMPLEX ON GUAM (NEUROPATHOLOGICAL MICROSCOPIC DATA)

| | *Case* 1 | *Case* 2 | *Case* 3 | *Case* 4 | *Case* 5 | *Case* 6 | *Case* 7 | *Case* 8 | *Case* 9 | *Case* 10 | *Case* 11 | *Case* 12 | *Case* 13 | *Case* 14 | *Case* 15 | *Case* 16 | *Case* 17 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A. Neurofibrillary changes: | | | | | | | | | | | | | | | | | |
| Frontal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Temporal cortex | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Sommer's sector | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Visual cortex | 0 | 0 | 0 | 0 | * | 0 | 0 | 0 | 0 | 0 | 0 | 0 | * | * | 0 | 0 | * |
| Amygdaloid nucleus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hypothalamus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Substantia nigra | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Periaqueductal area | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Brain-stem | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Inferior olivary nucleus | 0 | 0 | 0 | 0 | * | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Purkinje cells | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| B. Granulovacuolar bodies | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| C. Lewy's bodies | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| D. Pick's bodies | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| E. Senile plaques | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| F. Neuronal loss and gliosis | | | | | | | | | | | | | | | | | |
| Substantia nigra | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Globus pallidus | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hypoglossal nucleus | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | + | + | 0 | + | 0 | 0 |
| Anterior horn of spinal cord | 0 | 0 | 0 | 0 | | | 0 | 0 | 0 | 0 | + | + | + | 0 | + | | + |
| G. Inflammatory changes | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| H. Anæmic infarct | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| I. Demyelination of pyramidal tracts | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | + | + | 0 | + | 0 | + |

*Only one or two neurofibrillary changes were observed per slide.

fibrils were stained and doubly refractile, while others were not. Those which stained appeared red with silver impregnation, were positive with periodic acid Schiff (PAS), metachromatic, stable with hyaluronidase and stained with Alcian blue. These staining characteristics were the same as those of acid mucopolysaccharides. The fibrils were positive with coupled tetrazonium reaction, did not alter their colour significantly with dinitrofluorobenzene and performic acid, and were discoloured after benzoyl chloride treatment. These results correspond to the reactions observed in senile plaques. Those fibrils which did not stain with Congo red showed negative reactions to all the above-mentioned stains for mucopolysaccharides. The neurofibrillary changes in our series are also readily observed with hæmatoxylin-eosin, Nissl, or with Lendrum's phloxin tartrazine stains, but they are non-sudanophilic, non-metachromatic, weakly positive or negative with PAS, stained with Congo red, and doubly refractile when polarized light is applied. There are no typical senile plaques.

The distribution of the altered ganglion cells is remarkable in that they always appear in certain specific parts of the central nervous system in all cases (Table III). The most severely involved area is the pyramidal cell layer of the hippocampus, particularly Sommer's sector, and the presubiculum. The substantia nigra is usually so severely damaged that neuronal loss is the most prominent feature. However, some intraganglionic fibrillary changes are always found in the remaining cells of the craniomedial parts of this structure. The hypothalamus is also severely affected and the mammillary bodies are frequently the site of gliosis. The anterior perforating substance, the substantia innominata, and the amygdaloid nucleus are also intensely involved. The more moderately affected areas are the frontal cortex, especially the cingulate gyrus and frontal pole, the temporal lobe, particularly in its anterior portion, the ganglion cells around the third ventricle and aqueduct of Sylvius, and occasionally around the fourth ventricle. The quadrigeminal plate and third nucleus contain occasional fibrillary changes, as do the tegmentum of the pons and medulla oblongata. The dorsal nucleus of the vagus is more commonly involved than the other motor cranial nuclei. The locus cæruleus shows a severe loss of cells, but neurofibrillary changes are scant. The ganglion cells of the reticular formation present scattered fibrillary changes. The smaller neurones of the olfactory bulb and of the spinal cord show occasional neurofibrillary changes. The visual cortex and the Purkinje cells are free of these changes in most of the cases. The distribution of the involved cells is almost always bilaterally symmetrical (fig. 12). It is of interest to note that the lesions show a predilection for the limbic system. In general, most of the neurofibrillary changes in the cerebral cortex differ in shape from those in

the hypothalamus, amygdaloid nucleus, substantia nigra and brain-stem (figs. 13, 14).

Alzheimer's neurofibrillary degeneration of the ganglion cells is an essential feature, along with senile plaques, of Alzheimer's disease and of senile dementia. However, the neurofibrillary changes in Alzheimer's disease are predominantly cortical (Alzheimer, 1907; McMenemey, 1940), although subcortical nuclei may also be affected (McMenemey, 1958). Mutrux (1947) claimed that the neurofibrillary changes occur predominantly in the association areas, and Morel and Wildi (1952) and Schenk (1955) observed that the cortical areas of projection, both afferent and efferent, tend to be spared. These observations vary somewhat from our findings inasmuch as in our cases the changes are equally severe in the hypothalamus and brain-stem as in the cortex. In a patient with manifestations of Creutzfeldt-Jakob disease, Jervis *et al.* (1942) observed neurofibrillary changes, although as a rule they are not found in other cases of this disease. They have also been reported in subacute inclusion encephalitis by Malamud, Haymaker and Pinkerton (1950), and by Corsellis (1951). Trétiakoff (1919) and Foix and Nicolesco (1925) first described neurofibrillary changes in the pigmented cells of the substantia nigra and the locus cæruleus in cases of Parkinson's disease. Hallervorden (1933, 1935) studied 21 cases of postencephalitic Parkinsonism and observed neurofibrillary changes in the substantia nigra in all cases and in the tegmentum pontis in most of the cases. It was stated that similar changes in the cortical nerve cells were very rare. Neurofibrillary changes occurring in younger patients with postencephalitic Parkinsonism were further noted by von Braunmühl (1949). According to his study, the decreasing order of frequency of neurofibrillary changes is: substantia nigra, locus cæruleus, tegmentum pontis, corpora quadrigemina, hypothalamus, nuclei around the third ventricle, corpus Luysi, red nucleus, pallidum, corpus striatum, dentate nucleus, Ammon's horn, insula, and lastly, the rest of the cortex. Greenfield and Bosanquet (1953) studied 19 cases of idiopathic, 10 cases of postencephalitic, and 5 cases of atypical Parkinsonism, as well as 22 controls. They found neurofibrillary changes in the brain-stem without senile plaques in 9 cases of postencephalitic Parkinsonism and in one with amyotrophy, and in one case of idiopathic Parkinsonism. The authors felt that the neurofibrillary changes differed in some aspects from those found in the cortex and hippocampus in Alzheimer's disease. Greenfield and Bosanquet paid special attention to the midbrain and pons, but examination of the frontal or temporal cortex was not reported. However, they stated as follows: "Even in the case in our series in which paralysis agitans was combined with Alzheimer's disease no neurofibrillary changes were seen in the midbrain or pons, although they have been found there in other cases of Alzheimer's disease." Later, Beheim-Schwarzbach's (1954) study of "true" paralysis agitans

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showed neurofibrillary changes in the substantia nigra in 25 per cent of their cases.

Recently, Tatetsu (1959) reported on a clinico-pathological study of 13 cases of Parkinsonism, 3 of which had had a definite diagnosis of encephalitis in the past. All of his cases showed neurofibrillary changes in the substantia nigra, and 7 out of 13 presented these same changes in the diencephalon and brain-stem. In one of his cases, a patient who died at 29 years of age, psychiatric manifestations in addition to Parkinsonism were present; neurofibrillary changes were distributed widely in the central nervous system.

In spite of the different observations on this subject in the literature, it is interesting to find that neurofibrillary changes often appear in the brain-stem in some forms of Parkinsonism, predominantly postencephalitic, but without senile plaques.

Raskin and Ehrenberg (1956) in their review noted that Alzheimer or Alzheimer-like fibrillary changes have been reported in other conditions such as cholera, dysentery, pellagra, general paresis, and cachexia in man, as well as in various animal experiments.

(4) *Intracytoplasmic Granulovacuolar Inclusions*

Many of the ganglion cells in our cases contain round or oval granulovacuolar bodies in their cytoplasms. The size of these bodies varies from one to five microns in their greatest diameter. Almost all of them contain a central core which is strongly argentophilic and which stains strongly with hæmatoxylin. The peripheral zone is unstained, and it appears as a halo. These bodies stand out distinctly and are sharply outlined inside the cytoplasm. A ganglion cell may contain single, few or, occasionally, many of these inclusions. Frequently, the entire cytoplasm is occupied by these bodies, and some of the cells may even lack a nucleus. The granulovacuolar inclusions are noted occasionally in the same areas in which neurofibrillary changes are observed. However, in Sommer's sector they are exceedingly abundant. They appear as a rule in the ganglion cells which fail to show neurofibrillary changes. However, occasionally both changes appear in the same ganglion cells. The clear peripheral zone is not stained with PAS, toluidine blue, thionin, Mallory's phosphotungstic acid hæmatoxylin, luxol fast blue, Sudan and methylene-blue stains. We feel that these bodies resemble Simchowicz's (1911) "coarsely granular degeneration," and that they are the cells referred to by von Braunmühl (1957) and Greenfield (1958) as "granulovacuolar degeneration."

These bodies, described by Simchowicz (1911), are found to have a similar distribution in our series, in severe cases of senile dementia, in Alzheimer's disease and in some cases of Pick's disease (von Braunmühl, 1957). However, the nature of this form of

degeneration remains unknown. Greenfield (1958) pointed out that "the restriction of granulovacuolar degeneration to forms of senile dementia and almost entirely to one group of cells gives it a special interest." The constant occurrence of these bodies is one of the significant features in our cases. As described above, the pathogenetic relationship between these bodies and neurofibrillary changes is not clearly demonstrated morphologically in our series, although Morel and Wildi (1952) believe granulovacuolar degeneration of nerve cells to be an early stage in the process of "Alzheimerization" on the basis of histochemical studies of their material.

(5) *Other Neuronal Alterations*

Loss of Nissl substance, chromatolysis, eccentricity of nuclei and other ganglion cell changes are commonly observed. Loss of neurones is always present. In addition, binucleation, neuronophagia and satellitosis are not rare. The particular cell swelling and globular argyrophilic inclusions seen in Pick's cortical atrophy are not present in any of our cases. Neither are Lewy's intracytoplasmic concentric hyaline inclusion bodies found in the substantia nigra in any of our cases.

There is no typical senile plaque formation, although occasionally there are a few faintly argyrophilic coagulated structures, resembling early senile plaques. Perivascular plaques of Scholz were not found in any of our cases. The presence of senile plaques is the most constant histological feature in cases of presenile and senile dementia. Generally speaking, senile plaques are a much more common finding in senile cases than are neurofibrillary changes. Only a few exceptional cases are reported in the review by McMenemey (1958) in which there were numerous neurofibrillary changes without senile plaques: Raskin and Ehrenberg (1956) studied 270 cases of patients, ages 60 to 97 years, and found senile plaques in 171 instances, and neurofibrillary changes in 30 cases of which 24 had numerous neurofibrillary changes, and all but one had senile plaques.

There has been much discussion on the histogenesis of senile plaques and Alzheimer's neurofibrillary changes. The mechanisms underlying these changes remain to be clarified.

(6) *Loss of Neurones in the Globus Pallidus and Substantia Nigra*

Actual loss of ganglion cells is always found in the involved areas associated with severe neurofibrillary changes, granulovacuolar bodies and the other neuronal alterations. However, the globus pallidus and the substantia nigra show more noticeable scarcity of neurones than the other structures in most of the cases in our series. Since the early classical studies by Lewy (1913), Foix and Nicolesco (1925), Bielschowsky (1922), and Hassler (1938), the globus pallidus and the substantia nigra



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have been considered to be the site of the most severe ganglion cell damage in Parkinsonism. It is becoming increasingly clear that the substantia nigra is the most consistently involved area in any case of Parkinsonism, whether the idiopathic or postencephalitic form. Other nuclei, such as the locus cæruleus, may also be involved. In this respect, our findings are compatible with those reported in the literature. However, Lewy's concentric hyaline bodies are not present in any of our cases. These inclusions were found in 75 per cent of the cases of Parkinsonism, according to recent investigations by Lipkin (1959). In spite of conflicting reports, as stated previously, there is some indication that Lewy bodies and neurofibrillary lesions are mutually exclusive phenomena, the former being characteristic of the idiopathic and the latter of the postencephalitic type of Parkinsonism. It is of interest that while neurofibrillary changes are common in our cases, they are less numerous in the globus pallidus and caudal portions of the substantia nigra where the severest cell loss and reactive gliosis are most prominent.

(7) *Glial Reactions*

There is astrocytic gliosis in the involved areas of varying degree, consisting of proliferation of gemistocytic astrocytes and of glial fibres. Microglial reaction is also commonly observed. Subpial and subependymal gliosis is found in varying degrees and is particularly pronounced along the frontal horns and third ventricle. A small number of macrophages containing sudanophilic lipid are found around small vessels, in the cerebral substance and in the brain-stem including the pyramids. There are no inflammatory changes, neither lymphocytes nor plasma cells being found.

(8) *Nonspecific Changes Presumably Due to Ageing Process*

Accumulation of lipid granules in the ganglion cells is seen in various parts of the cerebral cortex, including Betz cells, basal ganglia, thalamus, inferior olivary nucleus, dentate nucleus, motor nuclei of the brain-stem and spinal cord. The staining characteristics of the lipid granules do not differ from those of ordinary senile cases (Fine *et al.*, 1960). The distribution of this change is identical with that of so-called "lipofuscin." Along with this phenomenon there is some accumulation of iron pigment in the neuroglia and microglia, particularly in the globus pallidus, substantia nigra and in other areas. Certain other changes, such as atheroor arteriolosclerosis and rare minute softenings due to circulatory disturbance, were observed in a few cases.

## Clinico-pathological Correlation

The presence of widespread severe ganglion cell alterations in the cerebral cortex correlates well with the clinical picture of an organic mental syndrome. Severe involvement of the pigmented cells of the sub-

stantia nigra and locus cæruleus in all cases, as well as additional neuronal degeneration of the globus pallidus, are compatible with the Parkinsonian syndrome. The clinical evidence of amyotrophic lateral sclerosis in some of the cases can be correlated with histological changes in the motor neurones, as well as with demyelination of the lateral columns of the spinal cord. Further study is being done on this latter aspect of the disorder.

In general, the pathology of Parkinsonism is not as well defined as the conspicuous clinical features (Heath, 1947; Schwab and England, 1958). It is, however, becoming increasingly evident that the most common lesions are found in the melanin-bearing cells of the substantia nigra and other parts of the brain-stem, in the globus pallidus, substantia innominata and adjacent parts. Of these, the lesion in the substantia nigra has been considered as the most significant pathological finding (Greenfield and Bosanquet, 1953). This is borne out in our series as well. However, Lewy's concentric hyaline inclusions were not observed in any of our cases in contrast to the cases of "idiopathic" Parkinsonism.

The presence of severe astrocytic gliosis and the lack of senile plaques are similar to those in reported cases of Pick's disease. However, the presence of depigmentation of the substantia nigra and lack of distinct lobar atrophy in our series contrast with the gross findings in Pick's disease. Abundant neurofibrillary changes are not a feature of the latter in the majority of cases reported in the literature (Pick, 1892; Malamud and Waggoner, 1943; Hassin and Levitin, 1941; Ferraro and Jervis, 1935).

In regard to the dementia, the presence of abundant neurofibrillary changes and intracytoplasmic granulovacuolar bodies resembles the pathology described in Alzheimer's disease. However, the lack of typical senile plaques and the severe involvement of the substantia nigra and other subcortical nuclei are differentiating features from Alzheimer's disease. for the same reasons, and particularly because of the neurofibrillary changes, our cases also differ from Pick's disease, as stated previously. For although Parkinsonism may on occasion accompany Alzheimer's disease, as in the report of Rothschild and Kasanin (1936) or Pick's disease as in the case described by Akelaitis (1944), our cases differ histologically from the latter.

The clinical symptomatology of dementia with extrapyramidal findings and sometimes with an amyotrophic lateral sclerosis syndrome most closely resembles the Creutzfeldt-Jakob disease. Widespread neuronal damage in our cases may resemble this disorder pathologically, but the presence of the intraganglionic fibrillary changes and the other neuronal alterations again distinguishes them from the original cases described by Jakob (1921), Davison (1932), and others.

It is our opinion, therefore, that in the cases of Parkinsonism on Guam we may be dealing with a different entity than is recognized in either the

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presenile dementia or the Parkinsonian syndrome occurring in other parts of the world. It is already noteworthy that all of the 17 cases examined during the past two years on this small island presented common neuropathological features. Moreover, they occurred exclusively among the Chamorro adults.

However, we feel that further study of these and additional cases may give us a key to a better understanding of the presenile and senile neuropsychiatric disorders as well as the Parkinsonian syndrome.

## Summary

A neuropathological study is reported in 17 cases of a neurological disorder manifested by a Parkinsonian syndrome with mental deterioration found among the natives of Guam. All of the patients were Chamorro adults. The duration of clinical symptoms was about four years and death occurred about the sixth or seventh decade of life. The main macroscopic neuropathological features are the presence of cortical atrophy, and depigmentation of the substantia nigra and locus cæruleus. The consistent finding on microscopic examination is wide-spread ganglion cell degeneration of the central nervous system. It affects primarily the cortex of the frontal and temporal lobes, Ammon's horn, amygdaloid nucleus, hypothalamus, globus pallidus, thalamus, periaqueductal structures, substantia nigra and tegmentum of the brain-stem. There are numerous intraganglionic fibrillary changes and scattered intracytoplasmic granulovacuolar bodies in the affected neurones of these areas. However, typical senile plaques are not found in any of the cases. In addition, there is a diffuse loss of ganglion cells of variable degree, most marked in the globus pallidus and substantia nigra. Reactive glial proliferation accompanies the neuronal involvement. White matter is relatively well preserved in contrast to a severe involvement of gray matter. Degeneration of motor neurones and bilateral demyelination of the pyramidal tracts are observed in those cases which presented clinically with features of amyotrophic lateral sclerosis. Analysis and discussion of these findings with respect to other forms of dementia and Parkinsonism are presented.

## Acknowledgment

The authors are indebted to Dr. H. M. Zimmerman, Chief of Laboratory Division, Montefiore Hospital, New York, for his invaluable help and encouragement in carrying out this research project. Dr. Anthony Fons, III, and Dr. Jan Cammermeyer, NINDB, provided many helpful suggestions in the preparation of the manuscript.

We wish to thank Dr. H. Shiraki, Professor of Neuropathology, Institute of Brain Research, University of Tokyo, School of Medicine,

Tokyo, for his helpful advice and preparation of many of the microphotographs.

This investigation was supported in part by grant No. 249 from the National Multiple Sclerosis Society, New York, N.Y.

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# THE ACUTE ENCEPHALOPATHIES OF OBSCURE ORIGIN IN INFANTS AND CHILDREN[1] [2]

BY

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A FORMIDABLE clinical problem is posed by the infant or child who becomes acutely ill with fever, stupor or coma and convulsions. This is a condition much to be dreaded for it strikes without warning or follows what might otherwise be considered a relatively trivial respiratory or gastrointestinal infection, a minor injury or operation. During the course of the neurological syndrome respiratory difficulty and circulatory collapse may be associated with an alarming worsening of the patient's condition. And, it may prove fatal within a few hours or days despite all known therapeutic measures; or, an even worse outcome is the subsidence of the acute symptoms leaving the patient permanently enfeebled both mentally and physically. Recovery, on the other hand, is not impossible, which encourages the belief that earlier diagnosis and a fuller understanding of the underlying disease process might lead to the discovery of some method of therapy or, more importantly, of a means of prevention.

At the present stage of our knowledge of nervous disorders of children it is possible to discern several diseases which may cause a syndrome resembling the one under discussion, but usually they can be distinguished from it by clinical data and appropriate laboratory tests. Thus meningitis and parameningeal infections (epidural abscess and subdural empyema), virus encephalitis and subarachnoid hemorrhage from ruptured saccular aneurysms and vascular malformations can be detected with reasonable certainty by their special clinical features and the characteristic changes in the cerebrospinal fluid. Hypertensive encephalopathy with

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[2]This project was supported in part by a grant from the Schweppe Foundation.

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acute glomerulo-nephritis may be identified by the invariable elevation of blood pressure and changes in urine. Uræmia, hypoglycæmia, diabetic acidosis, water intoxication, hypernatræmia and hypocalcæmia are attended by characteristic changes in the chemistry of the blood. Also intoxications with lead and other substances can usually be recognized by a combination of clinical signs and laboratory tests though individual cases may give rise to much difficulty, especially if the history is incomplete. The diagnosis of simple febrile convulsions or epilepsy, the most frequent cause of seizures and coma in infants, is usually based on the mere conjunction of one or more generalized seizures and an acute infection. Prompt return of consciousness and recovery constitute the final confirmation of its benign nature.

Once these several diseases or clinical states have been set apart by appropriate tests there remains, however, a group of patients whose illness does not conform to any of these recognizable states, and it is with these that we are primarily concerned. They differ from the above diseases with respect to certain clinical features and the absence of significant change in blood and urine. Seizures, if a part of the syndrome, may continue to recur, unlike febrile convulsions; and the extremities may become flaccid or rigid in either decorticate or decerebrate attitudes. Extensor plantar reflexes are present and may persist. Coma is often profound and pupillary abnormalities, loss of corneal and pharyngeal reflexes, irregularities in respiratory rhythm or arrest of respirations are not infrequent. The cerebrospinal fluid may be under increased pressure but it is otherwise characteristically negative. This less clearly defined category of disease, usually referred to as *acute toxic encephalopathy*, *acute nonsuppurative encephalitis*, *acute serous encephalitis*, *acute productive encephalitis*, *infantile diarrhœa with encephalitis*, or *acute brain swelling*,[1] has been the cause of death in 6 per cent of all infants and children coming to autopsy in the Massachusetts General Hospital (30 of 460 autopsies) during the past decade. It is because of its obscure nature, gravity and frequency of occurrence that we are prompted to undertake an analysis of the clinical and pathologic data in the following series of cases. A case of hypernatræmia, recognized clinically, and other examples in which, in retrospect, deranged water and electrolyte metabolism appeared to complicate the course of an encephalopathy of obscure origin are included to stress the relationship of these factors to the entire acute toxic encephalopathy problem. The results of our studies suggest certain pathogenic

[1]Of these many terms, acute toxic encephalopathy is probably the most applicable since, as will be seen by our case records, the possibility of a bacterial toxin acting on the brain arises in nearly every instance. Hereafter we have frequently used this term to designate the condition since it is in the everyday language of physicians. Until a bacterial toxin with neurotropic properties is identified, however, this term cannot be fully justified; hence it is not used in the title of the paper.

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mechanisms that may in the future be explored in both clinic and laboratory.

## Review of Previous Medical Writings

A review of the medical literature has proven to be an exceedingly difficult task for the case reports and the views and opinions of physicians on this subject are widely scattered in journals and books, often being hidden under unrevealing titles. Brief reference to this group of illnesses is to be found in nearly every comprehensive account of infectious disease written in the last century or two. And, to establish priority of description or to ascribe credit for the first report is, therefore, virtually impossible. Certainly one of the earliest and most informative references on the subject appeared in the latter part of the nineteenth century under the authorship of J. J. Putnam (1895) who had observed on the wards of the Massachusetts General Hospital a series of children, suffering from an ill-defined group of illnesses classed as influenza, with manifest symptoms of disorder of cerebral function. Realizing that there was no evidence of an inflammatory process in the brain, he postulated that the cerebral symptoms were due to the action of toxins elaborated in the course of a bacterial infection. Children were said to be more susceptible to these toxins than adults. No distinction was drawn, unfortunately, between acute toxic encephalopathy and acute hæmorrhagic encephalitis. Anderson (1923) and Brown and Symmers (1925) in informative articles again called attention to this type of encephalopathy and emphasized its abrupt onset, rapidly fatal course, indefinite connexion with infection, the rather general nature of the neurological symptoms and the swelling of the brain as the principal finding at autopsy. Brain, Hunter and Trumbull (1929) corroborated the existence of this category of disease and discussed its relationship to hæmorrhage encephalitic and perivascular demyelination (postvaccinal encephalomyelitis).

A summary of the many articles which contain documented cases of acute encephalopathy in children would be tediously repetitive, especially if all the clinical and pathological details were recalled. It is sufficient for our purpose to indicate the medical background against which this neurological syndrome has figured, and to state something of the main clinical and laboratory data and the most common neuropathologic changes.

Otitis media and mastoiditis were the initial or underlying illness in one of the cases of Grinker and Stone (1928) and in those of Borries (1948), Piquet (1947), and Paillas and Roche (1946); an upper respiratory infection or pneumonia in one of the cases of Grinker and Stone (1928) Hassin (1945) Zentay (1938), MacGregor and Craig (1934), Comby (1907), Bernheim and Bonnefoy (1933), and Barr and Silverstein (1937); acute exanthematous diseases, in some of the cases of Alajouanine *et al.* (1938), Ribadeau-Dumas (1925), Mosse (1926), Hutinel (1927), Ladet (1937),

Marquezy and Ladet (1938), Davison and Friedfeld (1938), Wigand (1941), Tyler (1957), Daghelie *et al.* (1932), and Ferraro and Scheffer (1932); pertussis, in the cases of Askin and Zimmerman (1929), Habel and Lucchesi (1938), Woolf (1956), Husler and Spatz (1924), Neuberger (1925), and Alajouanine *et al.* (1938); influenza, in the cases of Marquesy *et al.* (1953) and Alajouanine *et al.* (1938); gastroenteritis, infantile cholera or diarrhœa, in the cases of Finkelstein (1938), Anderson (1923), Brown and Symmers (1925), Low (1930), Citron *et al.* (1930), Forster (1940), Christensen and Biering-Swenson (1946), Schwarz, Goolker and Globus (1932), Bessau and Rosenbaum (1928), and Prader and Rossi (1949); scarlet fever, in some of the cases of Top and Gordon (1937), L. K. Sweet (1949) and Alajouanine *et al.* (1938); and diphtheria in the cases of Hall (1932), de Lange (1945) and Dolgopol and Katz (1950). DeVries (1960) noted that the syndrome under discussion is the usual neurological complication of vaccination in infants; in his post-mortem series of post-vaccinial reactions not a single instance of vaccination encephalomyelitis was observed in a child less than 2 years of age. The average age of all the recorded cases of acute toxic encephalopathy has been approximately 18 months with a range from $5\frac{1}{2}$ weeks to 12 years. The majority were less than 6 years of age and only two articles contain cases 8 years old or older. The most frequently occurring neurological symptom has been an impairment of the state of consciousness, this being present in every case. Convulsions were less common and were absent in some cases of Levinson and Saphir (1935) and in those of Belam (1934), Tyler (1957), MacGregor and Craig (1934) and Mosse (1926). Fever preceded the neurological symptoms in the majority of cases but was clearly absent in some, although after a series of seizures the patients were almost invariably febrile. Reference to either decorticate or decerebrate rigidity has been noted in less than half of all the cases. Respiratory embarrassment or hyperpnœa has been observed at some phase of the illness in more than two-thirds of them and circulatory collapse, except terminally, in only a few. The cerebrospinal fluid was under either normal or elevated pressure (the latter in most cases) and was usually acellular with normal quantities of protein. However, an unexpectedly large number of cases were reported to have pleocytosis of 10–100 cells per cu. mm., mostly lymphocytes (Anderson, 1923), Ferraro and Scheffer (1932), Marquesy *et al.* (1953), Barr and Silverstein (1937), and Forster (1940); and less often the protein content was elevated or a few hundred RBC were found. The chemical findings in the blood were seldom given in sufficient detail to be meaningful but no glaring abnormalities were noted in electrolytes. The duration of the illness was a few hours or days though complete recovery or survival with signs of brain injury were recorded in a few of the articles. The neuropathologic changes were remarkably uniform. Brain œdema, as shown by increase in brain weight, flat cerebral surfaces and small ventricles and congestion of small vessels

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with occasional perivascular hæmorrhages were the usual gross findings; and microscopic examination disclosed only evidence of dilated blood vessels, thickening and increased cellularity of small intracerebral vessels widened perivascular and pericellular spaces and necrosis of nerve and sometimes glial cells. Toxic agents, autonomic imbalance, impaired cerebral circulation, alkalosis, acidosis, hypoxia, hypocalcæmia and hypertræmia were believed to be the basis of the clinical and pathologic changes. The evidence for or against these factors seldom has been logical and convincing. Often enough one cannot, from the published account of the cases, be certain of the relative importance of several factors such as hypoxia, hyperthermia, dehydration, etc., or of the reliability of some of the laboratory data.

## Presentation of Cases

The clinical and pathologic data from 16 cases are summarized in Table I. The following illustrative cases serve to highlight various aspects of the problem.

*Case I*—M.G.H. 785999.

*Clinical data:* A 13-year-old girl was admitted in an unresponsive state to the Massachusetts General Hospital on August 20. Five days before entry, upon returning home from a long bicycle trip and having previously been in good health, she complained of headache and pain in the left ear and neck. Her temperature was 101° but a medical examination at this time was otherwise negative. She was placed on a liquid diet, given 60 mg. of aspirin and put to bed. The next day she was asymptomatic and afebrile.

Three days prior to admission she began to vomit and this continued during the following two days, as often as every half-hour. Her temperature ranged from 94 to 96° F. Because she was dehydrated, a salt water enema and 120 mg. of phenobarbital were given on advice of her physician. She then gradually became drowsy, restless, thrashed about in bed and made irrational remarks. Upon admission to a local hospital she received 120 mg. of phenobarbital, 50 mg. of demerol, 1000 ml. of Ringers solution, and 1000 ml. of 5 per cent dextrose and water. By 1.30 a.m. she was even more irrational and hyperactive, but within the next few hours lapsed into a coma. She was then transferred to the Massachusetts General Hospital.

On admission she was still restless but would not respond to painful stimuli. Respirations were deep and irregular though the rate was 26 per minute. Temperature was 99°, pulse 140 and blood pressure 155/100. Her eyes wandered conjugately from side to side; the left pupil was slightly smaller than the right but both reacted to light. The fundi were normal. There was no paralysis, the deep tendon reflexes were hyperactive but symmetrical, and there were ankle clonus and Babinski signs bilaterally. The neck was supple and there were no tonic neck reflexes.

The urine examination revealed no abnormalities. The white blood count was 7,750 with 70 per cent polymorphonuclear leucocytes and the hæmoglobin 12 mg. per 100 ml.; the blood pH was 7·28; carbon dioxide content 15·0 meq., sodium 143·7 meq., potassium 4·6 meq., and chloride 103 meq. per litre; the NPN was 18 mg., sugar 174 mg., phosphorus 1·5 mg., calcium 9·6 mg. per 100 ml. There was no level of salicylate in the blood. The cerebrospinal fluid was clear and under pressure of 440 mm. when the patient was completely relaxed; and on a subsequent puncture the initial pressure was 300 mm. of water. It contained no cells, the protein was 26 mg., the sugar 132 mg.

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per 100 ml., and bacterial cultures were sterile. The skull films were negative; the pineal was calcified but was not displaced. The electroencephalogram was diffusely abnormal with high voltage slow waves of 2 to 3 per second, and occasional sharp waves, occurring bilaterally. A ventricular puncture was attempted but the lateral ventricles could not be entered. The patient's condition did not change appreciably, and she died the morning after admission.

*Post-mortem findings.*—The only abnormality outside of the nervous system was a mild focal bronchopneumonia in the left lower lobe. Post-mortem blood cultures were negative.

The brain weighed 1,600 grammes (normal 1,350 grammes[1]) in the fresh state. The cerebral hemispheres were swollen and the convolutional surfaces were flattened. The dural sinuses and meninges were normal. There was herniation of the temporal lobes bilaterally (fig. 1, Plate XCVII). The ventricles appeared to be small but of normal shape and position. No significant abnormalities were found on study of microscopic sections.

*Comment.*—In this case the cerebral œdema was severe and death appeared to have resulted from temporal lobe herniation and mid-brain compression. Microscopic examination of the brain disclosed only agonal changes. The only definite metabolic abnormality during life was a moderately severe metabolic acidosis and suggested the possibility of an ingested acidifying agent or renal disease, but these were not corroborated by the history or ancillary laboratory data. The exact cause and pathogenesis of the metabolic disturbance could not be specified. Infection was not the primary abnormality in this instance.

The following case is strikingly similar in many of its aspects.

*Case II.*—M.G.H. 603818.

*Clinical data*—A 7-year-old girl was admitted to the Massachusetts General Hospital on March 11, in deep coma.

This child had been healthy until approximately a week before admission to the hospital when she developed a mild generalized headache and rhinorrhœa. She had improved after three days and returned to school. The morning preceding the day of her admission she vomited and complained of abdominal pain. Throughout the next twenty-four hours the vomiting recurred every 30 to 60 minutes. It ceased on the day of her admission but when examined at 11.00 a.m. by the family physician she was observed to be drowsy, limp, and said she felt sore in all her muscles. Later she became restless, cried and turned her head disconsolately from side to side. The restlessness was interrupted by periods of reduced responsiveness and flaccidity of limbs. Her level of consciousness rapidly and progressively lessened and by the time of her transfer to the Massachusetts General Hospital on March 11 she was unresponsive to all stimuli.

The initial examination revealed, in addition to a state of coma, rigid extension of the legs, flexion of the arms and tonic neck reflexes. The tendon reflexes were hyperactive and there were ankle clonus and Babinski signs bilaterally. Her temperature was 99·2°, blood pressure 95/50, pulse 154. The skin was dry and she appeared dehydrated. There were no other abnormal physical signs.

The cerebrospinal fluid pressure was 200 mm. of water after the removal of an unestimated quantity of clear fluid; it contained 2 white blood cells and 1 red blood cell per cubic millimetre, a total protein of 10 mg., chloride of 96 mg. and sugar of 111 mg.

[1]All normal brain weights given in this paper are from Coppoletta and Wolbach—*Am. J. Path.*, **9**, 55, 1933.

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per 100 ml. The specific gravity of the urine was 1·030; it contained a 1+ test for acetone but no sugar or albumin; abundant red blood cells, probably the result of trauma from catheterization, were found in the sediment. The blood sodium was 140 meq.; potassium 4·4 meq.; chloride 96 meq., and the $CO_2$ content, 21 meq. per litre; the sugar 107 mg. and NPN, 58 mg. per 100 ml. The peripheral white blood cell count was 14,000 with 85 per cent polymorphonuclear leucocytes.

Treatment consisted of 750 ml. of 1/3 normal saline and 500 ml. of a solution of multiple electrolytes[1] in 5 per cent dextrose and water given intravenously over an eighteen-hour period. The child's neurological condition remained unchanged until the afternoon of the second hospital day when peripheral vascular collapse occurred. The right lateral ventricle was punctured through a burr hole and the pressure found to be raised. During this procedure she stopped breathing and artificial respiration was initiated. Then a temporoparietal decompression was done bilaterally and the ventricles drained continuously through a catheter. The brain was "extremely swollen" (fig. 2). 25 ml. of 50 per cent sucrose and a tracer dose of $P_{32}$ were administered intravenously for subsequent radioautographic studies. After surgery the child was placed in a respirator. The systolic blood pressure was then 80, the pulse rate 140, and temperature, 96·8. Later, circulatory collapse recurred and she died at 8.00 p.m., thirty-three hours after admission. On the day of death the blood sodium value was 133 meq., potassium 4·4 meq., chloride 94 meq, $CO_2$ content 23 meq. per litre and the pH 7·48.

*Post-mortem findings*—There were no abnormalities on examination of the viscera except a mild, patchy, interstitial pneumonitis and minimal areas of atelectasis. Vacuolization and swelling of the epithelial cells of the proximal convoluted tubules of the kidney were observed and were assumed to be due to the administration of hypertonic sucrose before death.

The surfaces of the cerebral hemispheres bulged through the bony decompressions (fig. 3) and the brain tissue had become soft and obviously necrotic along the inferior and posterior aspects of these cranial apertures. The brain weighed 1,770 grammes (normal 1,260) and was greatly swollen. None the less there were neither temporal lobe nor cerebellar pressure cones. The leptomeninges were normal except for a few small collections of subarachnoid blood in relation to one part of the operative decompression.

On microscopic examination there was a striking congestion of small blood vessels but no thrombi were seen. Fresh red blood cells were seen in the perivascular spaces of many blood vessels and the subarachnoid space, but these changes may have been agonal or post mortem for there was no evidence of phagocytosis of red corpuscles. In microscopic sections of all parts of the brain the cytoplasm of the nerve cells was shrunken and pyknotic and the nuclei deeply stained. The oligodendroglia were swollen and many of the glia cell nuclei were excessively dark or pale. A few lymphocytes were seen in the subarachnoid space in a few sections, but no perivascular inflammatory changes were found. No other significant abnormalities were noted. Radioautograms from a thin section of parietal cortex by Dr. Louis Bakay reflected an abnormal degree of penetration of brain tissue by the $P_{32}$ isotope (fig. 4).

*Comment*.—As in Case I, the cerebral œdema was severe. It undoubtedly began early in the illness before hypoxia had occurred, as shown by the elevated CSF pressure, and appeared to have caused the respiratory failure and hypoxia with circulatory collapse which must have further contributed to the swelling. The changes consistent with anoxic

[1]Solution contained sodium 40 meq., potassium 35 meq., chloride 40 meq., phosphate 15 meq., and lactate 20 meq. per litre and represents the composition of multiple electrolyte solution referred to elsewhere in this paper.

encephalopathy seemed only to have been of a few hours' duration and probably occurred at the time of or after respiratory failure. The radioautographic studies were interpreted by Bakay (1959) as evidence that the disease had in some way interfered with functioning of the "blood-brain barrier." The pathogenesis of this is obscure but it is tempting to speculate that the brain swelling resulted from it. Unlike Case I, antecedent coryza or other infectious processes were conspicuously absent. In fact, signs of infection did not appear until terminally when a pneumonitis developed. Again the possibility of ingestion of some toxic substance or a metabolic disorder was suggested by the prominence of vomiting, though some of this may have been secondary to high intracranial pressure. However, the chemical constituents of the blood did not reflect any serious metabolic disorder. In view of the vomiting, abdominal pain and mental changes, the possibility of porphyria should have been considered and appropriate laboratory tests carried out, but viewing the case as a whole, this would seem to be an unlikely diagnosis. It should be noted that no seizures occurred in this or in Case I and in this respect they differ from the remainder of the cases.

*Case VII*—M.G.H. 933583

*Clinical data*—This 15-month-old white girl was admitted to the Massachusetts General Hospital on August 7, because of prolonged unresponsiveness following a Salmonella gastroenteritis complicated by seizures.

The infant was one of twins who had developed normally and had been well until five weeks before admission when she had tonsillitis and high fever. During this episode she had a short generalized convulsion and shortly thereafter the twin convulsed under similar conditions. Both infants recovered uneventfully and the patient was well until July 21, two weeks before admission, when severe diarrhœa and fever became manifest. Two days later she had a generalized seizure and was admitted to another hospital where on admission her temperature was 106° F., pulse 150 and respirations 30 per minute. The blood pressure was not taken but her skin was described as "cold and damp." There was considerable mucus in the nasopharynx and coarse rhonchi were heard over both lungs. She was unresponsive, exhibited roving eye movements and was having generalized convulsions. The latter were controlled with phenobarbital (60 mg. was given by rectal suppository and 30 mg. by intramuscular injection). There were no signs of meningeal irritation and the cerebrospinal fluid was acellular and was normal in all other respects. The pressure was not recorded. Stool cultures were positive for a Salmonella Heidelberg. The nasopharynx was suctioned and oxygen was administered. Within 30 minutes her colour was normal but shortly thereafter generalized seizures recurred and continued intermittently over the next several hours. An additional 30 mg. of pentobarbital and approximately 200 ml. of 5 per cent dextrose and 1/3 normal saline were given intravenously. During this infusion she had a transient episode described as "typical carpopedal spasm." Apparently the spasm ceased without therapy and did not recur, suggesting that it might have been an episode of decorticate or decerebrate rigidity. High fever and diarrhœa continued for the next two days. The peripheral white blood cell counts ranged between 8,000 and 10,000 with 50 to 75 per cent polymorphonuclear leucocytes on smear.

Fluid therapy was maintained at about 75 ml. per hour, calculated to replace the excessive fluid losses. In addition, streptomycin, penicillin and chloromycetin were

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given in adequate doses. Except for a calcium of 9·6 mg. and a phosphorus of 3·9 mg. per 100 ml. on July 24, the third day after admission, blood electrolytes were either not determined or not reported. After several days the acute illness subsided but she remained poorly responsive. On admission to the Massachusetts General Hospital she was afebrile, irritable, had a high-pitched cry and was poorly responsive to painful stimuli. The eyes were open but she did not follow a bright light nor blink to threatening stimuli. The eyes moved conjugately from side to side upon rotation of the head. The pupils reacted to light but with hippus. There was no facial asymmetry and swallowing was normal. Her legs were flexed at the knees and hips, the right arm usually flexed at all joints whereas the left was generally extended. There was generalized rigidity and increased resistance to passive manipulation of all extremities. Supporting reactions and movements of progression of the limbs could not be evoked. The reflexes were brisk and the plantar responses probably extensor bilaterally. Pinprick on both sides of the body provoked crying and poorly co-ordinated movements. The electroencephalogram was interpreted as abnormal because of diminution in the frequency and voltage of waves over the left hemisphere. Radiographs of the skull were negative.

In view of the slight predominance of signs on the right side and the possibility of a sagittal sinus occlusion and cortical vein thromboses, a dural sinogram was attempted on August 20. In so doing, a large subdural effusion of deeply xanthochromic fluid containing 2·7 grammes of protein per 100 ml. was uncovered on the left side. On August 24, approximately 30–40 ml. of similar fluid was removed after a left parieto-occipital craniotomy. No subdural membranes were identified. A small cortical biopsy showed extensive loss of neurones and astrocytic gliosis. The surface of the left cerebral hemisphere was several centimetres beneath the inner surface of the cranium and did not expand at operation. The next day 25 ml. of air was injected into the lumbar subarachnoid space and radiographs of the skull showed an accumulation of large amounts of air bilaterally over the surface of the cortex and slight dilatation of the lateral and third ventricles which were not displaced laterally. The patient did poorly and died on September 1, six weeks after onset of the illness.

*Post-mortem findings*—There were no significant abnormalities on the general post-mortem examination. The brain weighed 950 grammes (normal 950) in the fresh state. Remnants of a subdural membrane over the left cerebral hemisphere were still present. All gyri appeared somewhat small and the sulci wider and deeper than normal. This was especially true of the right occipital lobe. The leptomeninges were slightly thickened. A small hæmorrhagic depressed area in the left midparietal region was identified as the site of biopsy. On coronal section a slight degree of enlargement of all ventricular cavities was found (fig. 5), the left occipital horn being more dilated than the others. On microscopic study there was evidence of a diffuse encephalopathy with a loss of nerve cells and increase in fibrous astrocytes and microglial rod-cells in the cerebral cortex. These changes were most severe in sections from the temporal lobe and Sommer's sector of Ammon's horn was devoid of nerve cells (fig. 11). The small hæmorrhagic area in the left parietal lobe was surrounded by active macrophages and astroglia. Purkinje cells of the cerebellar cortex stained poorly and were diminished in number in the depths of the folia. Astrocytes of the Bergmann layer were slightly increased in number and size.

*Comment*.—The primary illness was a severe gastroenteritis resulting in high fever, seizures, probable aspiration and shock. An encephalopathy from which the patient failed to recover occurred as a consequence of anoxia sustained during the acute illness. A tendency to convulse with fever had been noted before the terminal illness and may have contributed

to the initial seizure and its complications. The subdural hygroma was of little clinical importance but its treatment almost certainly hastened death. Hypertonic dehydration was never established but this is a recognized cause of subdural hygroma in infants (Finberg and Harrison, 1955) and one suspects that it may have initiated the illness here.

*Case X.*—M.G.H. 687431

*Clinical data*—This 4-month-old girl was perfectly well until December 9 when she convulsed for the first time. This was followed by other convulsions which continued without interruption until her death twelve hours later. Prior to the first convulsion she was observed to be acutely ill and her temperature was 104° F. The family physician gave one injection of penicillin and sent her to the Massachusetts General Hospital where she arrived one hour after the first seizure. On admission she was found to be in status epilepticus, cyanotic and without measurable blood pressure. She was not dehydrated, and the anterior fontanelle was flat. The right pupil was 7 mm., and the left 5 mm., but both reacted normally to light.

The white blood cell count was 27,500 with 84 per cent polymorphonuclear leucocytes. The blood sugar was 100 mg. per 100 ml.; no other blood chemical determinations were done. Lumbar puncture was traumatic and subdural taps were negative. Five hours after onset of seizures, at 1.00 p.m., the infant began to have watery stools which contained mucus and blood. They were frequent and copious and continued until just prior to death. Throughout hospitalization, the infant did not void.

Despite supportive treatment, including oxygen, penicillin, streptomycin, aureomycin, 900 ml. of a multi-electrolyte solution, plasma, and nembutal intravenously, the patient died twelve hours after onset of the illness. Vomiting occurred just before death.

*Post-mortem findings*—The lungs were œdematous, atelectatic and the stomach contents were found in the tracheobronchial tree. There was an acute enteritis with congestion of the mucosa especially at the ileum, and a prominence of the Peyer's lymphoid follicles. Under the microscope sections were found to show moderate numbers of inflammatory cells within the mucosa. *E. coli* was cultured from the intestines and cerebrospinal fluid at autopsy.

The brain was not weighed. There were no gross abnormalities but on microscopic examination, the cortical nerve cells were shrunken and darkly stained with pyknotic nuclei, and the cytoplasm of some were frayed or vacuolated. Aside from the swelling of the oligodentroglia there was a rather prominent cellularity of the walls of many small blood vessels and scattered small collections of red blood cells surrounding some of these vessels; no other microscopic changes were noted. In particular, there was no evidence of meningitis or other inflammatory process.

*Comment.*—Again the neuropathological findings suggested acute anoxia, and probably they were the result of prolonged shock. Death was surely due to terminal aspiration, although it seems questionable that recovery would have been possible even it if had not occurred. The underlying disease process, as in Cases 5, 6, 7, 8 and 9, was an acute enteritis. However, it is clear that the first convulsion preceded the diarrhœa and there was no significant dehydration at the outset. The initial seizure may have been the result of toxæmia and fever and the subsequent seizures could have been the result of anoxic changes or of some other metabolic complication.

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*Case XIV.*—M.G.H. 959280

*Clinical data.*—This previously healthy 18-month-old girl was admitted to the Massachusetts General Hospital convulsing and unresponsive on February 14. On the day of admission she developed an upper respiratory illness with diarrhœa and vomiting. There was fever up to 102° F. Four hours prior to admission her temperature had risen to 104° and she had had a generalized seizure. The mother swaddled the infant in blankets and came to the emergency ward of the hospital where she was asked to wait with the patient until the arrival of a physician. A few minutes later the infant was found convulsing and was deeply cyanotic. The seizures were not controlled until one hour after admission even though 65 mg. of intravenous sodium amytal and 4·0 ml. of rectal paraldehyde were given.

Aspirated vomitus was recovered from the trachea through an endotracheal tube after which procedure the infant's colour improved. On examination her temperature was 104·6° F., respiration 52, and pulse rate 160 per minute. The patient was unresponsive with small, poorly reactive pupils, hyperactive reflexes, and bilateral Babinski signs. She was flaccid until disturbed, at which time an attitude of decerebration (all four limbs extended) was assumed. There were signs of bilateral otitis media and of pneumonia.

The lumbar puncture was traumatic, the cerebrospinal fluid containing 15,000 RBC, 3 lymphocytes and 3 polymorphonuclear leucocytes per cu.mm. The total protein was 82 mg. and the sugar 117 mg. per 100 ml. The fluid was sterile. The peripheral white blood cell count was 20,700 with 54 per cent polymorphonuclear leucocytes. *Staphylococcus aureus* was cultured from the left ear; urine cultures were negative. The serum sodium was 133 meq. and potassium 4·4 per litre; blood calcium 8·8 mg., phosphorus 8·3 mg. (after seizure), and NPN 33 mg. per 100 ml. The total protein was 6·7 grammes per 100 ml.

The patient was treated with Dilantin and sodium luminal as necessary for convulsions which occurred briefly on several occasions. Penicillin and chloromycetin were given for the infections which cleared promptly.

The patient gradually stopped convulsing and became more responsive although hyperactive reflexes, Babinski signs, sucking and grasping reflexes persisted. Three weeks after admission fever recurred and an aspetic meningitis developed. Coincidental with this, the serum complement fixation titre against mumps rose from 1: 8 to 1: 256. An exposure to mumps just before onset of the present illness was established. The aseptic meningitis cleared uneventfully.

Following discharge, the patient improved somewhat but has never regained the ability to sit, talk, or do more than follow a moving light with her eyes. At the present time, nearly three years later, she is waiting admission to a state school for the mentally retarded.

*Comment.*—Although the cause of initial seizures could not be established with certainty there was nothing inconsistent with the diagnosis of febrile seizures. The mumps meningitis was unrelated to the acute illness and it is easy to see where confusion might have arisen if the clinical and laboratory data had been less complete. Aspiration apparently developed prior to her arrival at the emergency room where its recognition and treatment were temporarily delayed. Also the seizures were prolonged and ventilation further impaired so that it is difficult to ascribe the encephalopathy to a single event. A severe degree of hypoxia was undoubtedly sustained; and although the patient survived the acute illness, she never recovered from its devastating effects.

In the following case the illness began in a similar manner but the potential seriousness of the situation was recognized early and emergency measures instituted. The full-blown syndrome with its dire consequences was averted.

*Case XV.*—M.H.G. 107889

*Clinical data*—This 26-month-old boy was well until the morning of admission, when he was noted to be febrile. He was given a "baby aspirin" and chicken noodle soup. The mother left the room and on returning a few minutes later, noted him to be unresponsive and convulsing. The child was brought immediately to the hospital, arriving about an hour later. On admission he was unresponsive, decerebrate, cyanotic, and showed marked retraction of the intercostal spaces during inspiration. An emergency tracheotomy was performed and the respiratory tract aspirated of food particles; following this procedure, breathing became easier and the colour returned to normal. Temperature was 102° F. Within a few hours, the infant was without neurologic signs but had bilateral aspiration pneumonitis and otitis media. The cerebrospinal fluid was normal. The bacterial flora of the nose and throat was normal. Treatment with penicillin, chloromycetin, and phenobarbital was followed by complete recovery. An electroencephalogram, done three weeks after the illness, was normal.

*Comment.*—A primary diagnosis of febrile convulsion complicated by aspiration of food particles seems appropriate. The necessity of the tracheotomy might be questioned but it certainly did no harm and may have been life-saving. Ventilation improved rapidly after this and hypoxia was certainly minimal.

The following case is of particular interest since the patient survived many years in a demented state after the acute encephalopathy.

*Case XVI*

*Clinical data.*—This 13-month-old girl of previously normal development and generally good health was admitted to a community hospital in coma. Twelve hours before admission she developed coryza and was described as "sleepy and out of sorts." She took her bottle throughout that day but two hours before admission vomited and then had a generalized tonic-clonic convulsion which persisted for two hours, being terminated finally by ether anæsthesia, administered at home by a local physician. Prior to this, approximately 3 quarts of fluid of unknown composition was given by enema. It is not known how much was retained.

On admission, the temperature was 104° F.; pulse and respiration were rapid (figures not given). The patient was comatose with rigidly flexed arms and extended legs. The deep tendon reflexes were generally hyperactive and plantar reflexes extensor bilaterally. The optic fundi were normal, pupils equal and reactive to light, and the eyes moved conjugately to rotation of the head.

Serum electrolytes were not obtained but blood sugar and non-protein nitrogen were normal. The white blood cell and differential counts were normal, as was the urine. Blood culture and Hinton precipitation test for syphilis were negative. Radiographs of the skull, chest and long bones were normal. A lumbar puncture done shortly after admission is said to have shown a normal cerebrospinal fluid pressure but actually it was not measured. The fluid was clear, contained 8 lymphocytes and was otherwise normal. During the subsequent four weeks, 5 lumbar punctures were done; the cerebrospinal fluid was normal in every instance.

The patient was treated with penicillin and phenobarbital. She was fed by gavage



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for weeks, after which she took food orally. She remained acutely ill with temperature ranging between 99° and 105° F., for two weeks. Brief, generalized seizures recurred daily during this period. She became increasingly responsive and within two to four weeks regained the ability to follow people and objects with full conjugate movements of the eyes. A spastic quadriparesis with tonic neck reflexes had become apparent by then. Whereas, prior to her illness, she could walk and speak a few words, she never regained the ability to speak, sit, or even to hold her head erect. As time passed, she improved somewhat. She acquired a friendly smile, especially when spoken to, made occasional pleasant but inarticulate sounds, but was unable to follow verbal commands or pantomime, and never manipulated objects with her hands. She withdrew from painful stimuli. Seizures posed no problem, though they did recur (generalized ones) at the age of 6 and 11 years. At the age of 13 years she was physically small, and her head measured only 46 cm. in circumference (normal 50–59 cm.). Death occurred as a result of bronchopneumonia twelve years after her acute illness.

*Post-mortem findings*—Bilateral bronchopneumonia was the only significant abnormality outside of the nervous system.

The brain weighed 840 grammes before fixation (normal 1,350 grammes). The major dural sinuses, cerebral veins and arteries were patent and of normal appearance. The leptomeninges over the frontal lobes were thickened and semi-opaque. The parietal, temporal and occipital convolutions appeared generally somewhat small, but those of the frontal lobes were strikingly atrophic, being one-third to one-half normal size and extremely firm on palpation (fig. 6). The sulci were widened as were those of the insula.

When sectioned after fixation there was extreme atrophy of the frontal lobes. Narrowing of the cortex and greyness of convolutional white matter was even more evident. In addition, the frontal white matter was reduced in bulk, and the corpus callosum was only one-third its normal width. The lateral and third ventricles were symmetrically dilated, about twice normal size. No definite gross abnormalities of brain-stem and cerebellum were noted.

There were microscopic abnormalities of the cerebral cortex in all major lobes of the brain. These were most severe in sections from the grossly atrophic frontal lobes where widespread neuronal loss was found. This was marked at the depths of sulci where in many sections there were no recognizable neurones (fig. 9). Astroglial nuclei were only moderately increased in number and no microglial hyperplasia was recognized. The involvement was not confined to the field of distribution of a single artery, vein or venous sinus and no thrombosed or recanalized vessels were found. The changes were comparatively slight in sections from the temporal, parietal and occipital lobes but even here definite islands of neuronal loss were observed. Involvement of Sommer's sector of the hippocampus was asymmetric, there being almost total devastation on the left (fig. 10) and only mild depopulation of neurones on the right. Changes in the cerebellum were minimal but Purkinje cells appeared more sparse than normal and the Bergmann layer of astrocytes was slightly increased.

*Comment*.—This case again emphasizes the complexity of the clinical problem. The first seizure was quite consistent with a severe febrile one. An excessive amount of fluid was given by enema and the subsequent coma and decorticate attitude could have been due to hypo-osmolarity of the blood, i.e. water intoxication, although blood chemistries to substantiate this were not obtained. The pathological findings indicate that the encephalopathy was of a destructive nature. Its cause remains obscure but hypoxia is most likely despite a somewhat unusual distribution

of the pathological changes. From the pathological findings alone an encephalitis could not be excluded, but the repeatedly normal cerebrospinal fluid during the acute illness would be strong evidence against such a diagnosis.

## Discussion

### A. *Nature of Clinical Syndrome*

The most common neurologic abnormality in the cases under consideration was an impairment of consciousness varying in degree from drowsiness, inattentiveness, and reduced awareness of stimuli to stupor and coma. Generalized convulsions were the next most prominent sign, being present in all except 3 cases. Other neurological findings, such as bilateral Babinski signs, loss of pupillary reflexes and paralysis of ocular movement or gaze, and decorticate or decerebrate postures, were less frequent. The cerebrospinal fluid was under either increased or average pressure and was normal with respect to cellular content, protein and sugar, except in the 2 cases in which an unexplained slight pleocytosis was found. The illness was of acute onset and fever preceded or accompanied neurologic signs in all but 3 cases. The duration of the illness was from one to several days. Irregularities of breathing were almost invariable and respiratory arrest was the usual mode of death although circulatory collapse also occurred when there was overwhelming infection or severe hypoxia.

Of considerable value in the differential diagnosis of this syndrome of acute toxic encephalopathy and the conditions with which it may be confused are certain negative data. Evidence of focal disease of the cerebrum or brain-stem was conspicuously absent in all of our cases. In fact from these clinical and pathological data it appeared that the presence of prominent focal signs should cast doubt on the diagnosis of acute toxic encephalopathy. Conceivably the heightened intracranial pressure could in itself be the source of a derangement of function in one part of the cerebrum through the mechanism of temporal lobe pressure cone, necrosis of one cerebral peduncle and occlusion of one or both posterior cerebral arteries but these changes were not observed in any of our series. It not infrequently happened that in the convulsive phase of the illness one or more unilateral or focal seizures appeared and may have led the examiner to suspect a lesion in one cerebral hemisphere. Usually, however, the inconstancy of their pattern and a shifting of seizures from one side of the body to the other, indicated the generalized nature of the disease process. The electroencephalogram was on occasion helpful showing that the electrical abnormality was bilateral rather than unilateral.

### B. *Pathologic Characteristics*

In reviewing published accounts of autopsied cases of acute toxic encephalopathy one cannot fail to be impressed with the diversity of pathological findings. The brains have varied macroscopically, some being

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normal in all respects, and others either swollen with flat surfaces, narrowed sulci, small ventricles and bilateral temporal lobe and cerebellar herniations or shrunken, sometimes with excess of subarachnoid or subdural fluid or pseudomembrane formation. Those cases with massive necrosis of cerebral cortex or of cortex and white matter have usually been excluded from this category of disease and instead are presented separately as examples of cortical degeneration or some other type of encephalopathy, but whether this division is entirely justified is open to argument. Microscopically the reports have ranged from "normal brain" to abnormal, the latter interpretation usually being based on capillary engorgement, perivascular and pericellular œdema, acute cloudy swelling, pyknosis or degeneration of nerve cells, focal collections of glial cells "œdema and thickening" of the leptomeninges, increased cellularity (usually "round cells" or histiocytes) of the meninges and proliferative arteritis or endarteritis of brain vessels (enlargement or increase in number of endothelial and adventitial cells).

The difficulties in accepting these microscopic findings as valid criteria of disease are known to all neuropathologists who have had experience with the brains of infants and children. Engorgement of small vessels, seen either grossly or microscopically, is common in all types of disease and related more closely to the mode of death (whether or not there was respiratory failure) than to any other factor. It is not then an identifying characteristic of any one of the diseases under consideration. The nerve cell changes reported as pyknosis, dark cell change, swelling, pallor or chromatolysis, "acute or severe cell change" probably represent at least two forms of cellular abnormality both of which also lack specificity, being frequently observed in the brains of infants or children dying of whatever cause (figs. 7, 8). One of these is the pale, swollen cell with frayed or fragmented cytoplasm and separation of the cytoplasmic and nuclear membranes by a clear space (fig. 7A). The cell looks to be hydropic. This series of changes is ubiquitous in the brains of infants and children and is probably due to the high water content of the infant brain and to the action of strong dehydrating agents in the preparation of microscopic sections. It cannot be accepted as a mark of cerebral disease. The other nerve cell alteration is the dark, "spiky" or pyknotic cell, often with shrinkage of the cell body and hyperchromatism of the nucleus (fig. 7B). Again it is observed in all human and animal material which has been handled before being placed in a bath of fixing solution (Cammermeyer, 1960) and is difficult to distinguish from the "ischæmic nerve and glial cell change" in which all the cells in the cerebrum or one part of it are shrunken, dark and frayed. The reports of Grinker and Stone (1928), Hassin (1945) and many others make no attempt to distinguish these artefactual nerve cell alterations from the more reliable cell changes of disease, hence it is impossible to evaluate their neuropathological findings. Pericellular and perivascular

clear spaces in microscopic sections, the tissue having retracted from cell borders and blood vessels, are another almost invariable finding. It is especially marked in the brain after formalin fixation and paraffin embedding and is much increased by post-mortem autolysis. Admittedly, necrosis of tissue (infarction or severe hypoxia) is accompanied by an increasing degree of tissue retraction during fixation and the difference is only quantitative. However, our experience with experimentally induced brain œdema has convinced us that tissue retraction is not a valid measure of œdema. The published illustrations do not permit even the most critical pathologist to decide whether this pericellular and perivascular retraction was due to post-mortem manipulation or hypoxic necrosis. We find, further, that it is seldom possible to decide in microscopic sections whether or not the connective tissue of the pia-arachnoid is increased in amount or in density; and the assumption that a given degree of separation of the fibrous tissue strands represents meningeal œdema is wholly invalid. Finally, it must be pointed out that the small vessels in the brains of children are more cellular than those of adults, an appearance which is often mistaken for vascular proliferation. The latter does, none the less, occur with all destructive lesions of the brain which call forth adventitial histiocytes. Again published illustrations of these vascular changes are seldom convincing.

In sum, the descriptions of neuropathologic changes in cases of acute toxic encephalopathy have been, almost without exception, a mere recounting of artefacts or changes that cannot be accurately interpreted in post-mortem material.

We have observed all these histologic alterations in our post-mortem cases but have observed that they do not differ from those seen in other cases in which death was not preceded by cerebral symptoms. They cannot, therefore, be accepted as characteristics of the disease or diseases under discussion. Far greater importance must be attached to the widespread shrinkage and cell alterations that were combined with reaction of microglial, astrocytic, vascular and meningeal cells, such as were observed in Cases 8 and 9, and assumed to be the result of hypoxic encephalopathy. Furthermore, in cases surviving for longer periods (Cases 7 and 16), disappearance of nerve cells with astrocytic gliosis could be taken as an infallible indication of a neuropathologic process, also probably of an hypoxic origin because of its distribution (Sommer's sector of Ammon's horn laminar and pseudolaminar nerve cell loss, loss of Purkinje cells in the deep folia of cerebellum (fig. 10)). In contrast, in other of our cases (1, 3, 6) in which the conventional Nissl and myelin preparations revealed none of these changes, the brain tissue could not be distinguished from control cases of similar age dying without neurological symptoms. Lastly in Cases 2, 4, 5, 10, 11, 12 and 13 most of the nerve and glial cells in the cerebral and cerebellar cortices were shrunken and pyknotic to a degree

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compatible with a recent severe hypoxia but in the absence of glial, vascular and meningeal reactions we were unable to interpret their significance. Whether or not the brain was swollen or œdematous (1, 2, 3, 4, 5, 11, 12 and 13), of average size and weight (Case 7) or small (Cases 6 and 16) proved to be unimportant, for size or volume did not reflect itself by any consistent microscopic change. Hæmorrhages when present (e.g. Case 10) were small and recent (no cellular reaction). We could only assume that they were agonal and probably related to hypoxia.

We must conclude, therefore, that no definite cellular or tissue lesion has been defined in acute toxic encephalopathy and that widespread destruction of neurones or of cerebral tissue, not infrequent findings in this material, correlated consistently with some complications of the illness such as hypoxia. Subdural hygromas with subdural fibrous membrane formation was observed in a single case of probable hypernatræmia as reported previously by others (Weil and Wallace, 1956; Finberg and Harrison, 1956).

### C. *Causes and Mechanism*

The precise cause (or causes) of this condition and its mechanism have not been previously ascertained, though several writers have assumed the presence of a toxin. It may be of some value, therefore, to scrutinize the clinical data from our cases to see if this or any other factors are suggested.

#### (1) *Bacteria or Bacterial Toxins*

It is clear enough from our case notes that each of the patients had become ill prior to the onset of the neurological disorder. In Cases 1, 4, 12, 14, 15 and 16 the initial illness was a respiratory infection and in Cases 5, 6, 7, 8, 9 and 10 it was a gastrointestinal disorder. In Case 3 rubeola was probably the primary disease. Only in Cases 1, 11 and 13 do the clinical data not permit the identification of the acute illness. Thus, in all except three of our cases, there was an antecedent infectious, febrile illness.

An analysis of the original infection fails to provide a clue as to how the infection could have induced the neurological disorder. Certainly it was not by means of the infective agent invading the brain; and if due to a toxin reaching the brain via the blood stream the neurological syndrome did appear to be related to the intensity of the infectious illness for in some it was mild even though the neurological disorder was severe. In fact the infective illness seemed not to differ in any particular way from the many similar illnesses that occur in infants and children without such neurological complications. However, not knowing the nature of the specific infectious agent or that all cases are alike in being due to a particular bacterial toxin, one cannot pursue this analysis to any further advantage. And there

must remain the possibility that certain bacteria have the power of elaborating an endotoxin which is harmful to the undeveloped nervous system. In fact already it is known that in experimental animals certain bacterial toxins exert powerful effects on the nervous system, e.g. Bridgwater *et al.* (1955).[1] And, finally, it is a common observation that there are individual differences in the reaction of infants and children to infections, some being more disposed to convulsions or delirium than others.

(2) *Fever*

Inasmuch as fever itself, the usual accompaniment of any infectious disease, may impair the function of the central nervous system in individuals of all ages but particularly in infancy and childhood, there is the possibility that this alone could have altered the nervous activity or have changed the brain. Body temperatures in excess of 106° F. are usually necessary to cause heat-stroke with its attendant seizures and coma and the common sequel of cerebellar ataxia. The body temperature was elevated to this degree in only 2 of our cases (Cases 4 and 7); in Cases 6, 9, 10, 12, 13, 14 and 16 the temperature rose to 104°–105°. Nevertheless, it must be conceded that fever of lesser degree has also non-specific adverse effects on the nervous system, this being especially obvious when some other cerebral disease (hæmorrhage, infarct, demyelinative lesion) coexists. This is especially true of infants and small children in whom it is known to precipitate seizures. This may, in fact, have been the agency responsible for their occurrence in Cases 5, 7, 9, 10, 11, 12, 13, 14, 15 and 16. Probably Cases 14 and 15 were the most informative in this respect for it seemed clear that a simple febrile seizure was the initial cause of the neurologic disorder and in the former case pulmonary aspiration probably had induced an anoxic encephalopathy from which the patient failed to recover. In several other instances it seems likely that a combination of these factors, i.e. fever, convulsion, respiratory disorder and hypoxia, had led to a fatal outcome. Fowler (1957) has stressed the potential seriousness of febrile convulsions, and reported post-mortem changes in a series of autopsied cases. The clinico-pathologic data from his cases suggested that hypoxia was the basis of the enduring signs of encephalopathy. The prominence of seizures with fever in the course of Shigellosis has been commented upon by Kowlessar and Forbes (1958), but whether or not the incidence of fever is higher in febrile states associated with enteritis, as contrasted with other illnesses, is not certain. Certainly respiratory infections and the exanthemata are responsible for the majority of febrile seizures in pediatric practice (Livingston, 1954).

Thus, it is impossible to distinguish between the effects of toxin and the fever which it induces in the causation of these neurological illnesses.

[1]This problem is under further investigation in our laboratories and the results of our studies will be the subject of a later report.

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Moreover it cannot be decided whether a constitutional predisposition to convulsions, i.e. to be susceptible to febrile convulsions, was of importance in our cases of acute toxic encephalopathy. Unfortunately this requires the comparison of two clinical states (acute toxic encephalopathy and febrile convulsions), the cause of neither of which is known; and the possibility of an identical mechanism for the two conditions can only be entertained but not proven until more is learned about one or the other of them. The same may be said of the relationship of acute toxic encephalopathy to the cerebral disorder known as febrile delirium.

(3) *Fluid and Electrolyte Imbalance*

The severity of the diarrhœa in Cases 5, 6, 7, 8, 9 and 10 raises the question of a major disturbance in fluid or electrolyte balance being the cause of the cerebral disorder. In Cases 6 the excessive administration of a hypertonic, alkaline solution resulted in hypertonic dehydration and alkalosis. In fact, the entire illness may be ascribed to this condition and to its treatment. Although less clearly documented, hypertonic dehydration was very likely present early in the illness of Case 7, and 12 may have been another example of hypertonic dehydration complicated by hypoxia.

In Cases 5 and 16 the administration of large amounts of tap water by enema suggests the possibility of water intoxication. The use of large amounts of hypotonic solutions certainly could have caused an encephalopathy with seizures but in neither instance were the necessary biochemical data obtained. Hence the diagnosis of water intoxication cannot be clearly established. However, even if it was present it could not have been the complete explanation, for some of the neurologic signs *preceded* the enemas. Changes consistent with hypoxia encephalopathy of recent origin were found in one of these cases (Case 5) and the extensive cortical damage in the other (Case 16) was also probably a consequence of hypoxia.

In Case 1 vomiting was exceedingly prominent but more likely it was the result of elevated intracranial pressure or some other factor and not the primary cause of the neurologic syndrome.

It may be concluded that fluid and electrolyte disturbances have not been incriminated as the primary factor in producing the clinical syndrome in the majority of cases. Nevertheless, there are some in which these are the major factors in the neurological illness, and further, it has been shown by a number of investigators that the infant and child are unable to manage an excess of fluid given orally, rectally or parenterally during infections or after operations when excessive amounts of circulating antidiuretic hormone may be present (Crawford and Dodge, 1959). These disturbances of salt and water metabolism are of special importance because they represent examples of treatable metabolic abnormalities. Only if one is continuously alert to their possible occurrence will they be distinguished clinically from other varieties of acute toxic encephalopathy.

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(4) *Hypoxia*

The frequent occurrence of hypoxia in these cases has been alluded to repeatedly. Impairment of ventilation in association with seizures and obstruction of bronchial passages by aspirated oral secretions or vomitus were responsible for the hypoxia in most cases but circulatory collapse due to infection or hypoxia added a factor of ischæmia to the hypoxic state in several instances. In no single case did hypoxia clearly precede the neurologic syndrome, hence it cannot be designated as the *primary* cause in any. In Cases 2, 7, 8, 9, 10, 11, 12, 13 and 16 the histopathological findings in the brain were of a type which is compatible with hypoxia. Case 14 is of particular interest in this regard for it would appear that hypoxia was responsible for all events of the illness that followed the initial febrile convulsion. This case and Case 15 illustrate the narrow margin which may exist between a simple febrile convulsion from which there is usually complete recovery and an irreversible anoxic encephalopathy. The potential danger of hypoxia during seizures has been remarked upon by a number of medical writers (e.g. Zimmerman, 1938; Fowler, 1957; and Millichap, 1960).

In general it may be said that fever, water and electrolyte disturbances and hypoxia are not the crucial factors in all cases of acute toxic encephalopathy. A nuclear group remain after these have been set aside in which some factor or factors must account for the disturbance in brain function. Our Cases 1 and 2 are illustrative for in them the neurologic illness developed and evolved in the absence of any of the above factors. The initial disorder was an obscure encephalopathy, possibly toxic. Brain swelling was the most consistent post-mortem finding and may provide the basis for the symptoms and signs which constitute the core of the syndrome. The small ventricles in the swollen brain indicated that increased intracranial pressure was clearly not due to an increase in the cerebrospinal fluid reservoir such as exists in hydrocephalus or in the state known as meningeal hydrops. Moreover, an increase in venous pressure or an elevation in the level of blood p $CO_2$, which are known to lead to vascular engorgement and a measurable increase in intracranial pressure (White *et al.* 1942; Austen, Carmichael and Adams, 1958), were not the cause of the brain swelling because at post-mortem examination the marked cerebral œdema was usually not accompanied by congestion of vessels.

The mechanism of the brain swelling in this condition has not been discovered. The interesting observation of Bakay (1959) (Case 2) of the rapid passage of $P^{32}$ into the brain suggests that function of the "blood-brain barrier" was impaired. Reports on the effects of hypoxia on this barrier are at variance; but the most recent studies of Bakay (1957) inform us that under certain circumstances at least, hypoxia permits $P^{32}$ and trypan blue to pass the endothelium and basement menbrames of cerebral vessels more easily than in the normal brain. Whether the reduced effect-

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iveness of the "blood-brain barrier" in this case was due to hypoxia or some unidentified factor cannot be stated, but it seems likely that once the barrier has been disturbed the capacity of the brain to maintain internal homeostasis as regards water and electrolytes may fail. The relative sensitivity of the barrier to trauma, infarction and various injurious substances has been studied (Bakay, 1956). We have recently found that its function may be altered in hypertonic dehydration (Dodge and Sotos, 1961).

In summary it can be stated that a single, common factor cannot be incriminated. Some few of the cases are due to water and electrolyte imbalance but the majority are not. Fever is important in nearly all of the cases and possibly the direct action of a bacterial toxin may be the initiating factor. The post-mortem data, which reveal no trace of cerebral invasion by an infective agent, are compatible with the toxin theory. The added factors of fever, convulsions, respiratory embarrassment and hypoxia are evidently operative in most of the fatal cases.

D. *Differential Diagnosis*

The full clinical syndrome of acute toxic encephalopathy is not difficult to distinguish from other forms of acute neurological diseases in infants and children. When the patient is seen early in the course of the illness, however, there are several possibilities which must be considered. A few comments concerning the most reliable means of separating these several conditions may help those who have had relatively little experience with this class of disease.

Since acute toxic encephalopathy may first be manifested by occurrence of a seizure it may be confused with a simple febrile convulsion, especially in the period of life from 6 months to 5 years. At the time of the first seizure or within the hour that follows it, there probably is no way of distinguishing these two conditions. An infection, a generalized seizure at the time of rising temperature, a lack of focal or lateralizing neurological signs are common to both of them, as is also the normal cerebrospinal fluid under a normal pressure. The first hint of some other form of acute encephalopathy occurs when the patient fails to regain consciousness after the expected length of time, the profound coma or other manifestations of disordered brain function persisting for hours or days. An elevated cerebrospinal fluid pressure in a relaxed patient, which occurs in some of the cases of acute toxic encephalopathy, tends to exclude febrile convulsions.

Encephalitis may be difficult to separate from acute toxic encephalopathy, especially during seasons when viral infections are known to be extant. A number of different infectious diseases which involve the brain may evoke a clinical picture which resembles that under discussion. These include malarial encephalitis, rickettsial encephalitis, infectious

mononucleosis, herpes simplex (acute inclusion body encephalitis), the equine and St. Louis encephalitides. Furthermore several of the better known types of meningitis may simulate the toxic encephalitis, e.g. tuberculous meningitis, ECHO viruses, lymphocytic choriomeningitis, mumps, etc., as well as postinfectious encephalomyelitis and acute necrotizing hæmorrhagic leucoencephalitis. Several of these diseases possess characteristic clinical features which cannot be discussed here for lack of space and, in addition, the cerebrospinal fluid exhibits changes of crucial importance, i.e. lymphocytic or neutrophilic leucocyte pleocytosis, increased protein, etc. It is under these circumstances that a case of acute toxic encephalopathy showing 10–25 lymphocytes per c.mm. in cerebrospinal fluid may baffle the most experienced clinician. Despite this occasional mild cerebrospinal fluid pleocytosis, which has proven to be an extremely rare laboratory finding, it remains a safe clinical rule at this stage of our knowledge to seriously question the diagnosis of an acute toxic encephalopathy whenever there is a significant cerebrospinal fluid pleocytosis.

The other identifiable forms of acute encephalopathy, such as those due to barbiturate or other drug intoxication, lead poisoning, liver disease, renal disease, diabetic acidosis and hypoglycæmia, may be distinguished by the clinical picture plus the chemical changes in the blood and cerebrospinal fluid. The cerebral disorder is nearly always generalized. In these conditions the cerebrospinal fluid is acellular. Lead intoxication is the only exception to this latter statement for it often includes a mild pleocytosis and an increased protein content.

Idiopathic epilepsy, i.e. status epilepticus, may resemble the syndrome of acute toxic encephalopathy. In fact, it seems likely that certain cases presently labelled acute toxic encephalopathy are actually examples of status epilepticus occurring as the initial convulsive illness in a patient without a previous history of seizures. Factors such as hypoxia may be responsible for death or permanent cerebral damage in both groups of diseases and no absolute criterion for distinguishing between them exists at the present time. A previous diagnosis of epilepsy at least partly resolves the diagnostic problem.

### E. *Factors which Determine Occurrence of Sequelæ in Surviving Cases*

Of the cases that survive the illness of acute toxic encephalopathy the degree of residual damage might be expected to vary from complete recovery (Case 15) to hopeless mental retardation and paralysis (Cases 14 and 16). As suggested earlier, the degree of brain damage and its irreversibility probably depend on the severity of hypoxia and ischæmia incurred during the course of the illness. The hypoxia may last only a few minutes and be overlooked. If brain swelling is pronounced, temporal lobe herniation may occur and interfere with the circulation of the midbrain and subthalamus, with devastating effect on the mechanisms which

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subserve consciousness. There may also be other factors which are responsible for the serious brain damage but at the present time these have not been clearly identified.

F. *Management of the Patient with Acute Toxic Encephalopathy*

Until the primary cause or causes of this syndrome have been identified, it will probably be impossible to outline an intelligent therapeutic programme. Conversely, once the causative factor or factors become known, steps may be taken to avert them and to halt their progressive action. At this stage of our knowledge the general lines along which therapy should proceed are becoming discernible.

The first part of the clinical study of any case is concerned with the exclusion of most of the specific conditions which may simulate the syndrome of acute toxic encephalopathy. Usually this requires little time and effort and is readily accomplished by means of a careful history and physical examination, including blood pressure, supplemented by the appropriate laboratory studies. Urine should be obtained if necessary by a catheter and that not used in routine examination and culture should be saved for chemical analysis of all possible toxic substances or metabolites which are abnormal either because they are present or are found in abnormal amounts. Keto-acidosis (diacetic acid), aspirin poisoning and intoxication with the phenothiazine drugs may be suspected from a positive ferric chloride test of urine. An indwelling catheter for the first few days may aid in maintaining an accurate balance of water and electrolytes. Blood culture, serum electrolytes, total solutes, blood urea nitrogen, sugar, and pH should be performed or measured and an "acute phase serum" obtained. If stored in the deep-freeze unit the serum is later available for serologic or toxicologic studies. Culture of the nose, throat and stool should be examined for pathogenic organisms. The pressure of cerebrospinal fluid should be recorded through a narrow gauge (22) needle and the cells counted, total protein and sugar measured; the fluid should also be cultured and when feasible some of it should be frozen in the event that further virological studies are indicated. X-rays of the skull and chest, if necessary, can usually be delayed until supportive therapy has been instituted.

Often patients with acute toxic encephalopathy arrive at the hospital in extremis and measures to maintain life must be begun while the diagnostic studies are progressing. When evidence of continued infection is obtained, therapy is logically directed towards the eradication of the bacterial agent by broad spectrum antibiotics, which should be administered as soon as appropriate cultures are taken. Moreover, an excessive febrile response needs to be suppressed because of its acknowledged adverse effect on nervous function. Barbiturate anticonvulsants tend to have an antipyretic effect but acetylsalicylic acid and cooling of body surface (aiming

to keep the rectal temperature below 102° F.) are more effective. Phetharbital (Millichap, 1960) which possesses both an antipyretic and anticonvulsant effect may prove to be of considerable value in such circumstances. The advantages of hypothermia are not at the moment sufficiently certain to recommend this difficult mode of therapy as a routine but they should be explored. Maintenance of a proper airway and adequate oxygenation of the blood are of paramount importance. Postural drainage is of value in accomplishing this and is technically easy in an infant, often being more effective than suction alone. Tracheotomy should be performed only if there is continued difficulty in keeping the airway clear. Supplementary oxygen by catheter or mask is a useful adjunct though in our experience it is no substitute for adequate pulmonary ventilation. If breathing fails, mouth to mouth insufflation until a suitable mechanical respiratory aid can be procured, may have to be employed.

The blood pressure must be maintained as near normal as possible. Usually falling blood pressure and failing circulation are due to hypoxia, fluid imbalance or infection. The combination of fever, hypoxia and hypotension appear to be extremely harmful to the brain. Fluids and electrolyte needs should be calculated and replaced by the intravenous route. They may be the means of counteracting the circulatory collapse caused by severe diarrhœa, vomiting and fever. Serum albumin is frequently depleted and replacement with albumin or plasma may help to maintain a vascular volume necessary for effective cardiovascular and renal function. The value of epinephrine, norepinephrine and similar drugs in improving cerebral circulation in shock has been questioned recently by Fazekas and co-workers (1960). They have shown that cerebral blood flow and oxygen uptake by the brain are increased relatively little when these drugs are used in treatment of shock. The theoretical possibility also exists that such drugs may increase the deleterious effects of endotoxins in man (May, 1960; Thomas, 1956). Nevertheless, in those cases in which the circulatory collapse does not respond promptly to other therapeutic measures, such drugs should probably be used.

Intravenous phenobarbital (100–300 mg. per sq. metre per day) combined with intravenous or intramuscular dilantin (200–400 mg. per sq. metre per day) are the basic anticonvulsants used. Rectal paraldehyde (15 ml. per sq. metre in mineral oil) is a valuable adjunct in some instances. If seizures fail to respond to these measures a general anæsthetic given by the anæsthesiologist may be necessary. It should be mentioned that persistence of mild myoclonic twitches of one or other part which do not impair breathing do not necessitate more intensive anticonvulsant therapy. A few seizures are probably less dangerous than oversedation.

Brain swelling with consequent elevation in intracranial pressure poses a major problem in many cases. When present, it dictates the need of measures to reduce this pressure because of the associated threat of brain-

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stem compression from bilateral temporal lobe or cerebellar herniation. Intravenous hypertonic solutions may be life-saving and of these the most effective are urea (1 gramme per kg. of body weight) (Javid and Settlage, 1956) and hypertonic sucrose, although admittedly they are not without some risks (Wise, 1960). An initial dose of urea may be repeated, being given either intravenously or by gastric tube. Treatment, previously mentioned, by hypothermia also reduces the intracranial pressure and does not have the potentially adverse effects of hypertonic urea on the serum electrolytes and on the "blood-brain" barrier (Dodge and Sotos, 1961), either of which may aggravate the pressure problem, and it may have a place in exceptional cases. Subtemporal decompression and ventricular puncture are therapeutic adjuncts which usually are not necessary. We have not been convinced of their efficacy and in many instances they are harmful.

Vigilant attention to every detail of therapy during the first days of the encephalopathy, with the physician being prepared to cope with every aspect of this multifaceted problem, seems to have assured the most favourable outcome. To anticipate complications of the sort detailed in this report is sounder than to combat them after they have occurred.

## Conclusions and Summary

The common neurological syndrome of children known as acute idiopathic or toxic encephalopathy and consisting of fever, convulsions, stupor or coma, decorticate or decerebrate postures and respiratory embarrassment has been observed in 16 patients, and the relevant clinical and pathological findings have been reported. In all except 2 cases the syndrome was engrafted on an evident febrile illness of variable type, the cause of which was seldom identified. Generalized convulsions were the dominant symptom, often ushering in the neurologic disorder and recurring throughout the acute phase of the illness. In a few cases, however, seizures were absent at all times and the principal nervous abnormality was an impairment of consciousness. The cerebrospinal fluid was typically clear and acellular but the pressure was elevated in the majority of cases. Breathing difficulty, ascribable to central derangement of respiratory mechanisms or to asphyxia from an obstructed airway, occurred in the majority of cases and was responsible for a complicating hypoxic encephalopathy. Circulatory collapse incident to infection and hypoxia was also a contributing factor. Disordered salt and water metabolism, resulting from the inadvertent enteral or parenteral administration of excesses of water or salt, or a lack of fluids and pernicious vomiting were noted in several cases. It took the form of either water intoxication or hypertonic dehydration. Although capable of producing a clinical syndrome almost indistinguishable from acute toxic encephalopathy, as in two of the illustrative cases, nevertheless we do not believe this to be the central problem.

At autopsy (14 cases) a swelling of the brain was found in all except 3 cases (two long-term survivors and one with hypertonic dehydration) and the œdema was not reflected in any consistent microscopic change. Indeed, except in those cases in which hypoxic encephalopathy supervened, no definite cellular or tissue changes could be found. The essential pathology of this condition must, therefore, be of a type not visible with the light microscope.

From an analysis of our clinical and pathological material it may be concluded that the disorder under discussion is an acute encephalopathy, separable from a primary systemic electrolyte or fluid abnormality, arterial or venous thrombosis, meningitis and encephalitis. In all probability, it is closely related to febrile convulsions and febrile delirium. The fatal issue or permanent disability appear to be determined by hypoxia or ischæmia of brain tissue. In other words, among several factors there are *at least* two operating in all the fatal cases: a primary one which is unidentified, possibly toxic; another, which seems to be secondary and is hypoxic. These two factors lend themselves to further clinical and laboratory investigation. Suggestions are offered for the management of this illness and for preventing serious brain damage.

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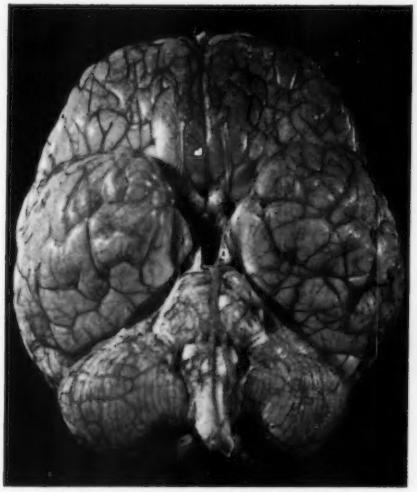

FIG. 1.

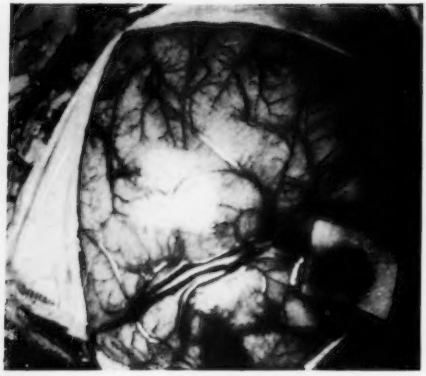

FIG. 2.

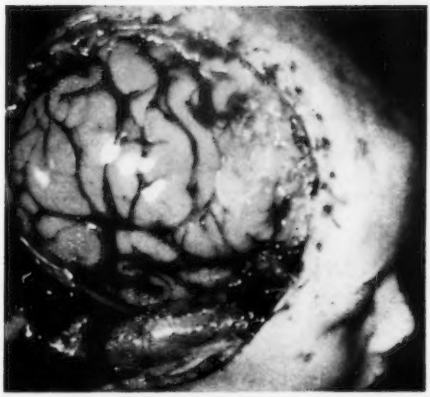

FIG. 3.

*To illustrate article by Gilles Lyon, Philip R. Dodge and R. D. Adams.*

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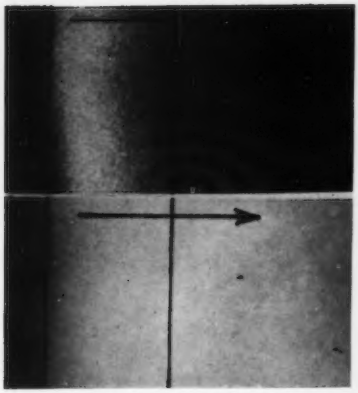

FIG. 4.

FIG. 5.

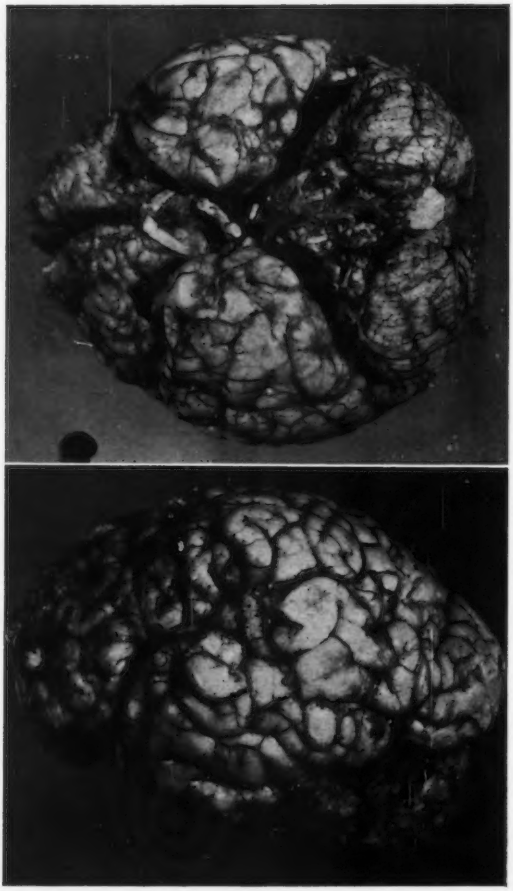

FIG. 6.

*To illustrate article by Gilles Lyon, Philip R. Dodge and R. D. Adams.*

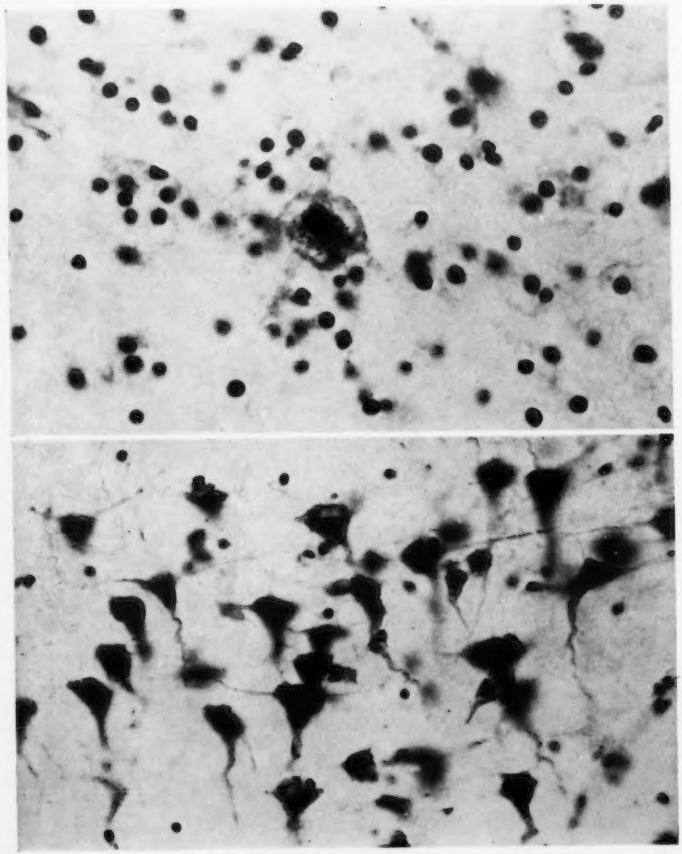

FIG. 7.

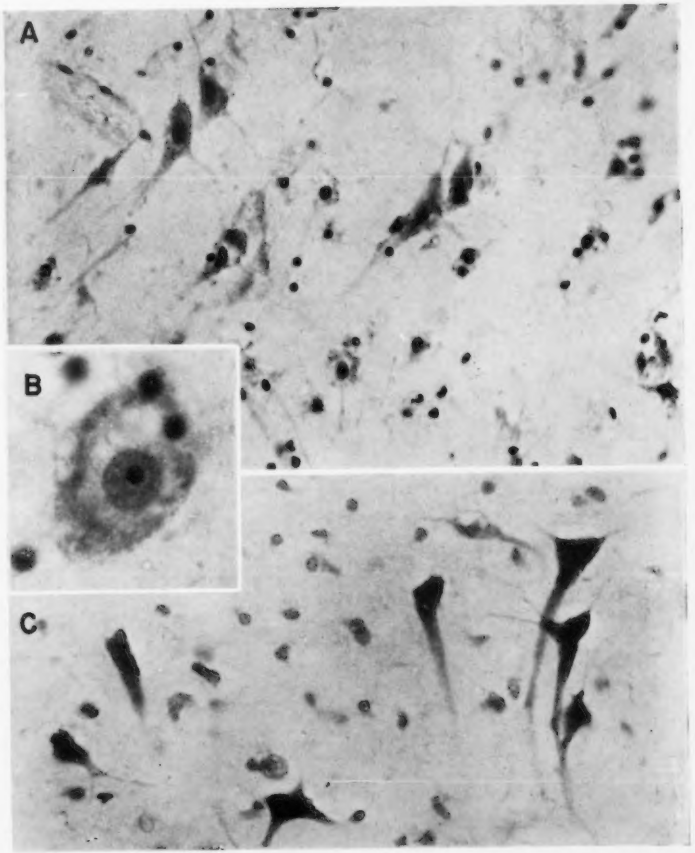


FIG. 8.

*To illustrate article by Gilles Lyon, Philip R. Dodge and R. D. Adams.*

PLATE C

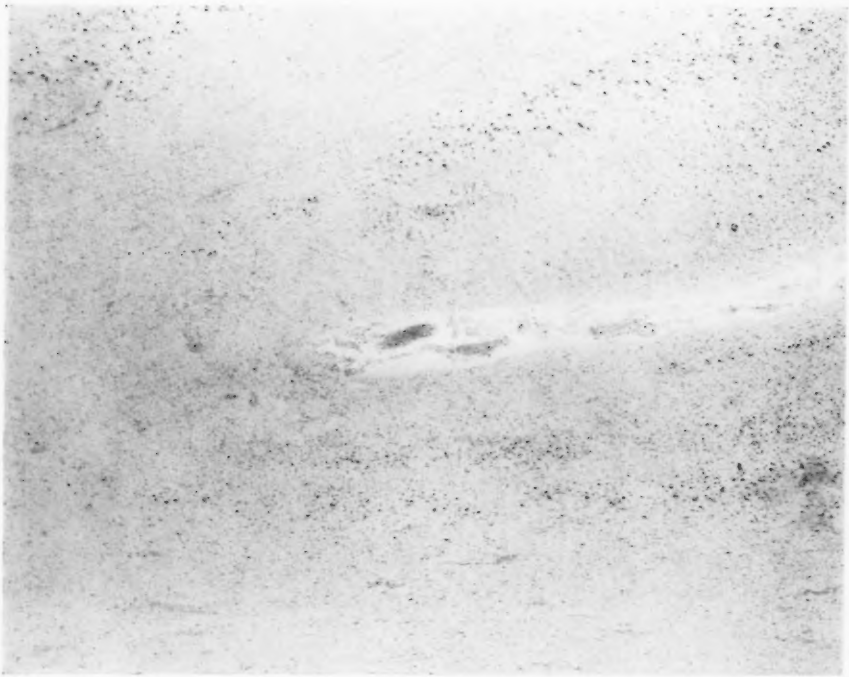

FIG. 9.

*To illustrate article by Gilles Lyon, Philip R. Dodge and R. D. Adams.*

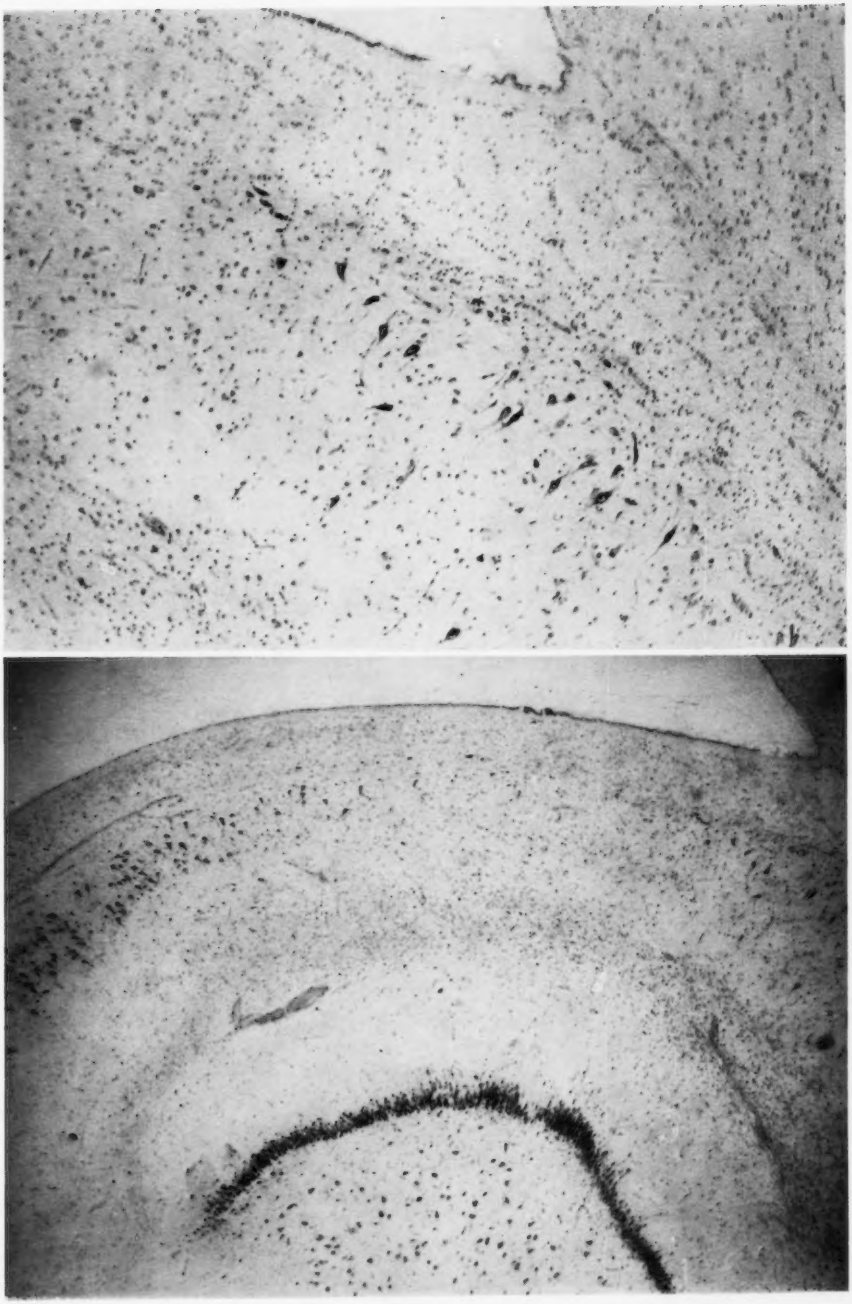

FIG. 10.

*To illustrate article by Gilles Lyon, Philip R. Dodge and R. D. Adams.*

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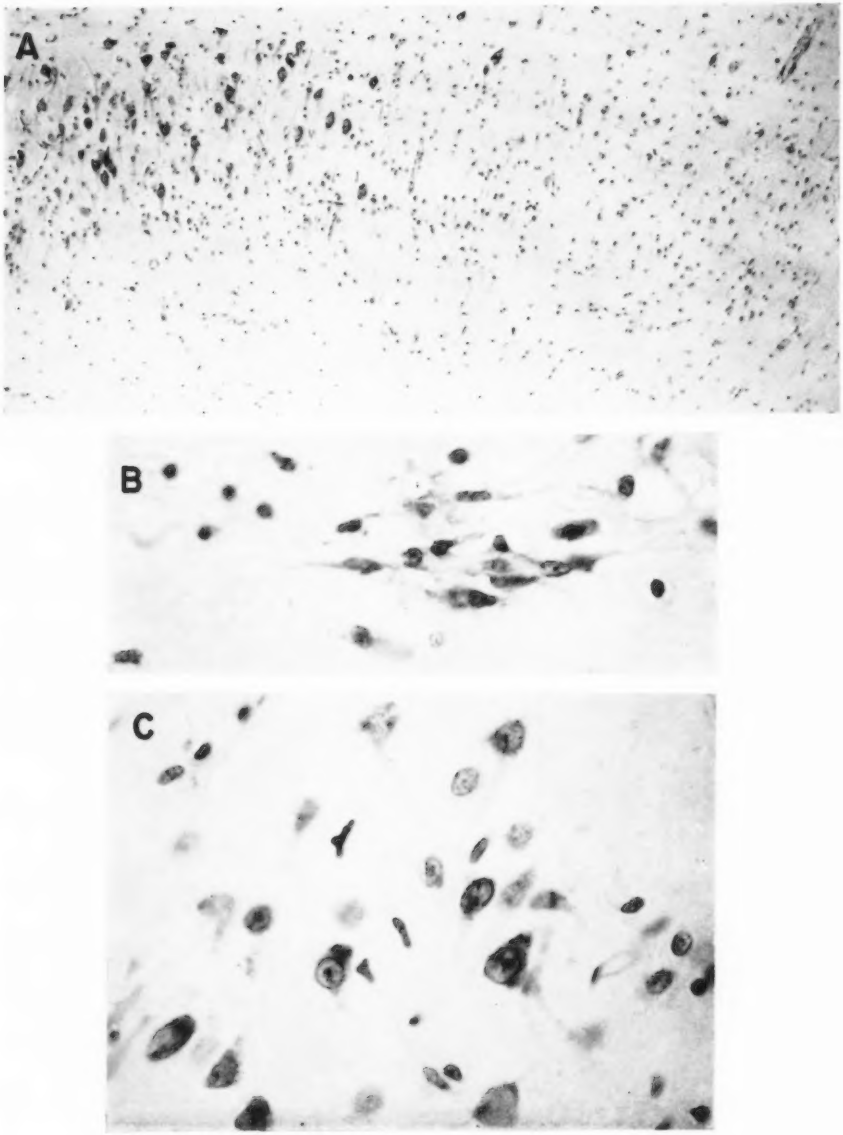


FIG. 11.

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## LEGENDS FOR PLATES

### PLATE XCVII

FIG. 1 (*Case* 1).—Ventral surface of brain, showing generalized swelling and grooving of mesial aspect of the temporal lobes. The mass of herniated temporal lobe is greater on the right side.

FIG. 2 (*Case* 2).—Appearance of the right cerebral hemisphere at craniotomy, demonstrating vascular congestion and brain swelling.

FIG. 3 (*Case* 2).—Marked bilateral herniation of swollen brain tissue as seen at post-mortem examination.

### PLATE XCVIII

FIG. 4.—Radioautographic prints of parietal cortex from a normal (upper panel) and Case 2 (lower panel), four days after the intravenous injections of 2 m.c. of $P^{32}$. Area between the vertical lines represents width of the cortex. Arrows indicate the direction of isotopic diffusion. Increased permeability of the blood-brain barrier is suggested by the appearance of the lower radioautograph. (From Bakay, L. (1959) *Neurology*, **9**, 18. Reprinted with the permission of the author and the Lancet Publications Inc., Minneapolis, Minnesota.)

FIG. 5 (*Case* 7).—Coronal section through the lenticular nuclei demonstrating slight ventricular enlargement and the absence of brain swelling. The site of brain biopsy is marked by an area of hæmorrhagic necrosis in the right parietal cortex.

FIG. 6 (*Case* 16).—Ventral and left lateral views of brain showing marked atrophy of frontal cortex and overlying leptomeningeal thickening.

### PLATE XCIX

FIG. 7.—Appearance of swollen, vacuolated neurone and oligodendroglial swelling (upper panel) and shrunken, dark staining neurones (lower panel) from the cerebral cortex of control infants dying without neurological symptoms or signs. Cresyl violet ×450.

FIG. 8 (*Case* 2).—Early necrosis of cortical neurones and glia. (A) Cortical neuronal changes comparable to those illustrated in fig. 7 were observed in this case also (B, C). In addition, early microglial and astroglial activation is noted in C. Hæmatoxylin and eosin ×450 (A, C) and × 970 (B).

### PLATE C

FIG. 9 (*Case* 16).—Illustration of the diffuse loss of nerve cells of the frontal cortex with virtual absence of neurones at the base of a convolution (left side of photograph). Cresyl violet × 35.



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## PLATE CI

FIG. 10 (*Case* 16).—Absence of nerve cells in Sommer's sector of the left hippocampus (lower panel). The right upper portion of this photograph is enlarged in the upper panel. Cresyl violet × 35 and × 80.

## PLATE CII

FIG. 11 (*Case* 7).—The upper panel (A) shows the loss of nerve cells in Sommer's sector of the left hippocampus. Cresyl violet × 80; in the middle panel (B) a cluster of microglia is seen surrounding a degenerated hippocampal neurone. Cresyl violet × 450; and in the lower panel (C) an increase in microglia and astroglia is shown in another area of damaged hippocampus. Cresyl violet × 450.

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# NOTICES OF RECENT PUBLICATIONS

## SENSORY DEPRIVATION AND ITS IMPLICATIONS

*Space and Sight. The Perception of Space and Shape in the Congenitally Blind Before and After Operation.* M. von Senden. Translated by PETER HEATH with appendices by A. H. RIESEN, G. J. WARNOCK and J. Z. YOUNG. 1960. Pp. 348. London: Methuen & Co. Ltd. Price 42s. net.

*Sensory Deprivation. A Symposium Held at Harvard Medical School.* Edited by PHILIP SOLOMON, M.D., JACK H. MENDELSON, M.D., PHILIP E. KUBZANSKY, Ph.D., RICHARD TRUMBULL, Ph.D., P. HERBERT LEIDERMAN, M.D., and DONALD WEXLER, M.D., with a foreword by STANLEY COBB, M.D. 1961. Pp. 262. Cambridge, Massachusetts: Harvard University Press. Price 46s. net.

The first of these two books is a study of the perception of space and shape in the congenitally blind, and the effects upon it of operations which give them sight. The author's review of the literature is extensive, and his conclusions are of great interest, though, as the appendices show, not in all respects beyond criticism. von Senden believes that the congenitally blind man has no *a priori* awareness of space, nor does he acquire it from sensations of localization on his skin, or from the kinæsthetic sensations accompanying the movement of his limbs or the concomitant muscular sensations. Guided by his constant communication with the sighted, the blind man, by a process of interpretative thought, "builds up his environment progressively in time, as a network of relationships." The resulting schemata, it is stressed, are the products of his attention to the relation of events in time, and have nothing spatial about them. The space concepts of the blind man are therefore intellectual achievements only, yet this logical and interpretative ordering of things is "accomplished by touch."

When such a person acquires vision, his first impressions are of brightness and colour, the colour patches being seen as extended, and in a uniform middle distance. When the colour patches are consciously identified as visual objects, they also begin to be consciously located in space. Gross differences of depth are perceived, and practice leads to a developing estimation of depth. Objective space is not a primary datum, but only secondarily acquired from subjective space. The idea of shape is not due to a mere dynamic effect of the stimulus on the visual organs, but is the outcome of a process of conscious interpretation in time. The final development up to the fully formed idea of shape involves a series of transitional forms as intermediate stages, which develop one from another, and are liable to vary between individuals, since it is the individual who himself creates them.

It must obviously be difficult to infer from such exceptional circumstances as those which attend the acquisition of sight by an individual who has grown up without it, what happens in the normal development of awareness of space. von Senden's denial of spatial qualities to all perceptual modalities except vision is hard to accept. If it be true, it must mean that awareness of the position and movement of limb seg-

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ments, for example, is not given in the sensory impulses from the limbs, but only in some way acquired by correlating these with experiences gained through vision. Nor does the fact that a congenitally blind person, who has acquired vision, cannot at first identify tactile shape with visual shape necessarily imply such a view. Moreover, von Senden appears to take no account of the vestibular system as an important contributor to our awareness of the orientation of the body in space. Nevertheless, whether one can go all the way with the author or not, the book is a most useful collection of facts, which psychologists, and philosophers concerned with perception cannot afford to neglect, and which are often also relevant to the work of neurologists, particularly in relation to visual functions and the agnosias.

It is some years now since the publication of the first studies of the effects of sensory deprivation upon man and animals. The Harvard Symposium comprises a number of papers dealing with various aspects of this question, including some of its practical implications, for example, the effects of sensory deprivation in aviation. It was at first startling to realize the extent to which normal consciousness depends upon the inflow of normal environmental stimuli ranging from the simplest sensations to communication with our fellows. As Dr. Stanley Cobb points out in the foreword to this book, the recent advances in the neurophysiology of consciousness and attention have established a framework into which these new facts can readily be fitted. Their remoter implications have perhaps yet to be realized, for, besides the rather dramatic experiments of subjects cushioned as far as possible against the impact of every kind of stimulus, there are many people who have to adjust themselves to blindness, deafness and other sensory deprivations produced by disease, as well as the wide range of environmental variations which man can now produce artificially. This useful book sets out the main psychophysiological facts which have emerged from recent experiments, and discusses some of their implications.

RUSSELL BRAIN.

## NEUROBIOLOGY

*International Review of Neurobiology*. Ed. C. C. PFEIFFER and JOHN R. SMYTHIES. Vol. I. 1959. Pp. 383. London: Academic Press. No price.

The authors summarize the intentions of this new review thus: "The Review covers the whole field of neurobiology and includes work within a particular basic science as well as in neurology and psychiatry. Particular emphasis has been laid on the recent development of ideas of fundamental importance and general interest and also of ideas from these basic fields likely to further our understanding of nervous and mental disease. In the past neurobiological sciences have played no little part in progress towards these ends. They are most active at present and they hold great promise for the future. The purpose of this Review is to contribute something to this objective."

The present volume is most valuable in this regard, containing a series of detailed reviews, in each of which a subject is submitted to critical scrutiny, the literature integrated, and periodic summaries made and conclusions drawn. As several of the eight reviews are of first importance they should be mentioned individually. They are:

Recent Studies of the Rhinencephalon in Relation to Temporal Lobe Epilepsy and Behaviour Disorders by W. R. Adey; Nature of Electrocortical Potentials and Synaptic Organizations in Cerebral and Cerebellar Cortex by Dominick P. Purpura; Chemical Agents of the Nervous System by Catherine O. Hebb; Parasympathetic Neurohumours; Possible Precursors and Effect on Behaviour by Carl C. Pfeiffer; Psychophysiology of Vision by G. W. Granger; Physiological and Biochemical Studies in Schizophrenia with Particular Emphasis on Mind–Brain Relationships by

Robert G. Heath; Studies on the Role of Ceruloplasmin in Schizophrenia by S. Martens, S. Vallbo, and B. Melander; and Investigations in Protein Metabolism in Nervous and Mental Diseases with Special Reference to the Metabolism of Amines by F. Georgi, C. G. Honnegger, D. Jordan, H. P. Rieder, and M. Rottenberg.

DENIS WILLIAMS.

*Works of the Institute of Higher Nervous Activity. Academy of Sciences of the U.S.S.R.* Programme for Scientific Translations. 14 Shamman Street, Jerusalem. 1960.

Physiological Series, in two volumes. Vol. 1. Cat No. 69. Pp. 461. Price 74s. Vol. 2. Cat No. 71. Pp. 374. Price 64s.

Pathophysiological Series, in three volumes. Vol. 1. Cat No. 70. Pp. 494. Price 78s. Vol 2. Cat No. 72. Pp. 399. Price 78s. Vol. 3. Cat No. 74. Pp. 393. Price 78s.

This series of very large volumes has been translated from the Russian through the services of the National Science Foundation of the United States of America. Volume 1 of the physiological series is concerned with experimental investigations in animals, largely on conditioned reflexes, conditioning in men, and cortical electrophysiology. Volume 2 deals with sensory activity in man, behaviour in man, electroencephalography, and autonomic activity in man. In the pathophysiological series, volume 1 deals with research into physiological changes in the psychoses; volume 2 with similar work in children; and volume 3 with work upon the activity of the nervous system in experimental intoxications and infections in animals.

There are a large number of independent papers by many senior authors, and each paper has a bibliography which, being in English, is an excellent introduction to the Russian literature upon that subject.

Access to the voluminous and official material is simply through the list of contents which is quite beyond the scope of an inclusive review, but the volumes, which must be of first importance to specialists in the abnormal physiology of nervous disease are available in the National Hospital.

DENIS WILLIAMS.

*The Nature of Sleep.* A Ciba Foundation Symposium. 1961. Pp. 416. London: Churchill. Price 50s.

Most of the twenty papers in this volume, which follows the well accepted Ciba pattern of presentation, deal with cellular electrical activity in the cortex. There is elegant work with intracellular microelectrodes and recordings from single cells from Oxford, Freiburg and Bethesda; discussion of the effects upon this cellular activity of modification of the brain-stem activating mechanism; and observations on the electro-encephalogram in experimental and natural sleep. The only concession to traditional speculation is an essay in the nature of dreaming, at the end of a volume certain to keep neuronal physiologists wide awake.

DENIS WILLIAMS.

## PSYCHIATRY AND PSYCHOLOGY

*Manuel de Psychiatrie.* By HENRI EY, P. BERNARD and CH. BRISSET. 1960. Pp. 1014. Paris: Masson et Cie. Price 100 NF.

The vitality of contemporary French psychiatry is attested by this large and well-organized textbook. It reflects the erudition, experience and balanced outlook of the senior author, who tells us in his preface that he tried to guard against too individual or one-sided a presentation by calling to his aid two collaborators—one from the mental hospitals, the other a psychoanalyst; but the stamp of his own comprehensive knowledge and luminous mind is clearly evident throughout. Inevitably the reader

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is reminded of Ey's learned Etudes Psychiatriques and of the nomumental section of the Encyclopédie Médico-Chirurgicale which he edited. This text has the merits of concision and orderly presentation. Due regard is paid to the findings and views of psychiatrists of other countries; and although here and there a claim is more definitely made for particular forms of treatment, or a biochemical feature is postulated more confidently than would be conceded in this country, on the whole there is a notable freedom from partisan statements.

In the first part of the book the history and contemporary trends of psychiatry, clinical and laboratory methods of examination, and general symptomatology are dealt with. The clinical section, which makes up the greater part of the book, describes the various syndromes, their causes, development, pathology and treatment. Mental defect is briefly sketched, and particular attention is given to the organic causes and accompaniments of mental disorder. A special section is devoted to psychotherapy and the more drastic or elaborate methods of physical treatment.

AUBREY LEWIS.

*Recent Progress in Psychiatry.* Volume 3 (*J. Ment. Sci.*). 1959. Pp. 397. London: J. & A. Churchill. Price 42s.

The present volume of reviews ranges widely over the basic sciences in their application to mental disease, from Genetics (Valerie Cowie and Eliot Slater) to the most physical of all, Surgery (Murray Falconer and Peter Schurr) with Ross Ashby discussing Cybernetics half-way between. Derek Richter reviews Biochemistry and Jonathan Gould contributes at length upon the difficult subject of the Enzymatic basis of some psychoses. The late Professor Alexander Kennedy has written upon Alcoholism and addiction, clearly and well, with Dr. Fish.

The fourteen reviews cross and recross the artificial boundaries between neurology, psychiatry and their related fields.

DENIS WILLIAMS.

*Psychiatrie. A Textbook for Students and Doctors.* By KURT KOLLE. 5th ed. Pp. 418. Stuttgart: Georg Thieme Verlag. Price DM 29.80.

This book, whose author holds the chair of psychiatry at Munich, has been deservedly popular. It is broadly eclectic, undogmatic and highly readable. The sections dealing with the psychoses are excellent. There is a very good chapter on normal and abnormal sexual behaviour, which is usually neglected in textbooks of this type. Students and medical practitioners should find the introduction into psychotherapy helpful, but the section dealing with the common neuroses is much too short and uninformative. Another chapter which requires to be brought up to date is that on child psychiatry. These shortcomings are rather serious because the neuroses and the behaviour disorder in childhood are of greater importance to the general practitioner and to the psychiatrist working outside the mental hospital than the psychoses. The strong bias in favour of the psychoses is rooted in the tradition of continental psychiatry. It might have been one of the reasons why the study and treatment of the neuroses developed outside the university departments.

E. STENGEL.

*The Structure of Human Abilities.* By PHILIP E. VERNON. 2nd ed. 1961. Pp. 208. London: Methuen. Price 30s.

This well-known survey of factorial studies of human ability first appeared in 1950. The present edition is unchanged apart from a few minor corrections and the addition of a chapter dealing with developments in the subject over the past ten years.

In Professor Vernon's view, the use of factorial methods does not entail "the

ascription of human abilities and behaviour to hypothetical faculties, traits or powers of the mind." For him, an ability (or factor) is no more than "a class or group of performances" and is to be admitted "only if a number of measurements in this class (e.g. test results) overlap or correlate positively with one another." If one agrees with this very sensible view, it is plain that factorial analysis cannot disclose the ultimate structure of human intelligence. Its purpose would seem rather to make possible a rational classification of abilities which may be applied with some confidence for educational or occupational purposes.

Although this book contains little of direct concern to neurologists, it may be strongly recommended as an admirably clear and balanced account of its subject. It should be borne in mind, too, that factorial analysis, if used with discretion, may well have its part to play in unravelling the complex patterns of disability due to injury or disease of the brain.

O. L. ZANGWILL.

*Handbook of Abnormal Psychology*. Ed. H. J. EYSENCK. 1960. Pp. 816. London: Pitman. Price £6.

This informative, if unwieldy, volume is dedicated to the memory of Emil Kraepelin, "who first applied the methods and theories of experimental psychology to the problems of abnormal behaviour." Although Kraepelin's flirtation with experimental psychology was short-lived, he seems never to have quite forgotten Wundt's "brass instruments" and their bewitching promise. For this reason, one may surmise that he would have approved of much in this book, not least its editor's fanatical devotion to the austerities of science. One may doubt, however, whether he would have appreciated the disdain for traditional psychiatric method so apparent in its pages.

The book is divided into three main parts. The first deals with sensory, motor and intellectual disorders, and their study by means of psychological tests. The second is concerned with causes and determinants of abnormal behaviour, special attention being paid to genetical and constitutional factors and to some aspects of conditioning and learning. The third part is concerned with the study and modification of behaviour by means of drugs, E.C.T. and psychosurgery. The editor himself offers a characteristic chapter on the effects (or lack of effects) of psychotherapy.

The editor has chosen his team of contributors (18 in all) almost wholly from those who have been associated with him in the work of the psychological department of the Maudsley Hospital. Although it is always invidious to single out individual contributions for special mention, the present reviewer would like to express his appreciation of the chapters dealing with heredity and psychological abnormality (Slater and Shields), childhood upbringing and related issues (O'Connor and Franks), and the psychological effects of electroshock (Campbell). Dr. V. Meyer contributes an erudite chapter on the psychological effects of brain damage which, unfortunately, is a little remote from neurological reality.

This book contains much useful and well-assembled information and should have real value as a work of reference. It is doubtful, however, whether it will fulfil the editor's intention of providing the blueprint of a scientific discipline upon which psychiatry can build. The terms of reference are too narrow and the methods totally inapplicable to a vast range of clinical problems. There is also far too little appreciation of the medical and social implications of the subject. None the less, the editor deserves warm commendation on his venture, which will no doubt become the Bible of Maudsley-trained clinical psychologists for many a year.

O. L. ZANGWILL.

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## PAIN AND NERVE BLOCKS

*Pain.* By F. J. J. BUYTENDIJK. Pp. 190. Hutchinson. Price 25s.

The first Duke of Marlborough's wife, Sarah, asked Voltaire to help her write her memoirs. Finding that he was an honest man and unwilling to tamper with the truth, she wrote, in a fury: "I thought the man had sense; but I find him at bottom either a fool or a philosopher." Certain national characteristics remain the same over the centuries; and the conjunction of fool and philosopher in the Duchess of Marlborough's mind makes us chuckle, because somewhere, partially hidden, there is an echo of it in our own minds, even though we are separated by two centuries. To a practical Englishman, nowhere does philosophy seem more out of place than in a book on pain. Here one needs action; one demands to be informed what to do about the pain, how to stop it; to do this, one has to know what causes pain, where it is felt, where it arises and all mechanisms of pain.

This book on pain contains no information. If it had been published before the war it might have been considered up to date; but as the chapter on the physiology of pain refers to no work done later than 1940 and as most of the references are to work done in the 'twenties and 'thirties, one cannot understand why the book has been translated into English and published here in 1961. Not only is the book outdated and therefore unsuitable for anyone, but one cannot understand for whom it was originally written. Who needs to be told that "the octopus is a kind of cuttlefish," and who would gain information by being told, "Anything touching a peripheric nerve which has pain fibres causes pain, or anything touching the deep roots of the spinal cord"? On the other hand, we would like to know the evidence which allows the author to tell us that "among many zoologically lower animals, consciousness is dim" and that "The consciousness of the octopus might be said to be clearer than that of the carp or even the cow." And if "dermatologists are aware of the remarkable relationship between itch and sympathetic innervation," may we not share in this esoteric knowledge?

No doubt the great philosopher of the generation succeeding the Duchess shared the national prejudice; for Hume advised us when we are faced with certain kinds of philosophic books: "If we take in our hand any volume of divinity, or school metaphysics, for instance, let us ask: Does it contain any abstract reasoning concerning quantity or number? No. Does it contain any experimental reasoning concerning matter of fact and existence? No. Commit it then to the flames. For it can contain nothing but sophistry and illusion."

P. W. NATHAN.

*Clinical Applications of Diagnostic and Therapeutic Nerve Blocks.* By J. Bonica, M.D. 1960. Pp. 354. Oxford: Blackwell Scientific Publications. Price 70s.

The American books that Blackwells bring out in this country are characterized by excellent printing and a high standard of production. This useful work by Bonica is another example of such first-class book production; it is indeed all one might expect for the high price. But the book would be more useful and presumably it would be bought by more people if it were cheaper and shorter. This could easily be achieved by proper editing; for the book is unnecessarily wordy throughout and it contains paragraphs of platitudes: such as "It is essential for the physician to make, confirm, or reject the diagnosis. . . . Even if the diagnosis is obvious, it is advisable that the physician investigate the problem fully," and so on, by the yard. The book has one other defect: the author has a general tendency to regard conjectures which are reasonable or likely as definitely known to be true facts. The section of the book on myofascial pain syndromes is particularly valuable.

P. W. NATHAN.

## MULTIPLE SCLEROSIS

*A Biochemical Basis of Multiple Sclerosis.* By ROY L. SWANK, M.D., Ph.D. A Monograph in American Lectures in Living Chemistry. Ed. I. Newton Kugelmass, M.D., Ph.D., Sc.D. Pp. 88. Figs. 14. Tables 2. Bibliography and Index. Oxford: Blackwell. Price 40s.

This small well-produced volume is primarily a review of the author's and other relevant literature in order to convince the reader that the author's hypothesis as to the pathogenesis of multiple sclerosis is the correct one.

It is suggested that the suspension stability of the blood is altered, that there are aggregates of red cells and that as the blood brain barrier breaks down toxic substances can act on this region. A review of patients on a low fat diet is used to support this view.

These suggestions, even if at variance with the views of many others, are put over very well but would not be accepted by all.

Few actual mistakes can be found in the text and the production is of the high standard which one associates with Charles C Thomas.

J. N. CUMINGS.

## SHORTER NOTICES

*Cerebral Palsy in Childhood and Adolescence—a Medical, Psychological and Social Study.* Ed. J. L. HENDERSON. Pp. 403. London: Livingstone. Price 35s.

A survey has been made of the population of "spastics" in the Eastern Hospital Region of Scotland. Professor Henderson directed it, and had in his team, in addition to the conventional medical specialists, administrators, an educational psychologist, social workers, a sociologist and a dentist. They studied all aspects of the subjects' handicaps, educational and social as well as mental and physical, and they surveyed the facilities available for them in the Region.

As the incidence in school children was more than two per thousand, the problem is a large one. 40 per cent of these children had a slight handicap, 35 per cent moderately severe, and 25 per cent a severe handicap.

The intellectual level was quite low, a quarter having an I.Q. of more than 85, another quarter between 70–85, the rest below, mental defect being twenty times higher than in the normal population. A quarter had epilepsy.

The report is loaded with detailed facts and much wisdom, and will be a source of study to the lay and medical workers in cerebral palsy. The team have presented the results of a meticulous survey lucidly and attractively.

*Modern Scientific Aspects of Neurology.* Edited by J. N. CUMINGS, M.D., F.R.C.P., Professor of Chemical Pathology, Institute of Neurology at the National Hospital, Queen Square, London. 1960. Pp. 360. Edward Arnold (Publishers) Ltd. Price 65s. net.

This volume, as the preface states, is mainly devoted to studies in the basic sciences which are related to the discipline of neurology. It therefore covers a wide field and covers the results of applying the newer techniques of physics and chemistry to both normal and abnormal states of the nervous system. L. Einarson writes on nucleic acids as structural constituents of the nerve cells, and C. Coers on nerve endings in striated muscles. There are several papers bearing upon the lipids, P. B. Diezel writing on the lipidoses, and Professor Cumings himself on abnormalities of lipid chemistry in the cerebral lipidoses and demyelinating conditions, while E. Klenk and H. Debuch write on the glycero-phosphatides and sphingolipids of the brain. Myelin

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and its breakdown are the subjects of chapters by F. Seitelberger, F. S. Sjöstrand and J. B. Finean, while R. H. S. Thompson writes on the esterases and D. Richter on epilepsy and the convulsive states. The book is well produced and illustrated and should fulfil the editor's hope "that the practising neurologist may obtain new information which is related to his subject."

*Memory Learning and Language.* Ed. WILLIAM FEINDEL, M.D. Pp. 69. Oxford University Press. Price 16s.

The University of Saskatchewan celebrated its fiftieth anniversary with symposia. Five of the staff and Dr. Penfield gave short addresses to the students on some aspects of neural functions serving mind, published here.

*Hysteria. Reflex and Instinct.* By ERNEST KRETSCHMER, M.D. 1961. Pp. 162. London: Peter Owen. Price 30s.

Kretschmer's late monograph has been translated by Vlasta and Wade Baskin. In it he presents his views upon the basis of hysteria in the organisms instinctive and reflex mechanisms, some of which have inherent survival value.

*Virus Meningo-encephalitis.* Ciba Foundation Study Group No. 7. 1961. Pp. 118. London: J. & A. Churchill. Price 12s. 6d.

The contributors to this symposium have been well and widely chosen, and the fifteen essays, with a meticulous bibliography, cover the field completely.

*Pathology of the Nervous System. A Student's Introduction.* By Professor J. HENRY BIGGART, *C.B.E.* Third Ed. 1961. Pp. 368. London: E. & S. Livingstone. Price 40s.

So complete in itself is this well-illustrated little book, and so carefully revised in this third edition, that it can be used by those working in neurology as well as by the student for whom it is intended. Each chapter has an excellent concise bibliography for those who want to travel farther.

*Essential of Neurosurgery, for Students and Practitioners.* By SEAN MULLEN, M.D. Pp. 273. New York: Springer Publishing Co. Price 6·75 dollars.

Those wanting a nodding acquaintance with the rudiments of neurosurgery will find them succinctly stated here. The little text is practical, but it is only intended as a most elementary primer.

*Stoke Park Studies Mental Subnormality.* (Second Series.) Ed. by J. JANCAR, Pp. 135. Bristol: John Wright. Price 30s.

The twelve essays in this volume collected by the staff of the Stoke Park Hospital include statistical studies of the performance of different groups of subnormal children, in which Dr. Fraser-Roberts has taken part, a series of therapeutic studies by Dr. Heaton-Ward and Dr. Jancar, and neuro-pathological reports by Dr. R. M. Norman and Dr. H. Urich. The first series was published nearly thirty years ago, and the second constitutes a Memorial Volume for the World Mental Health Year.

*The Integrative Action of the Nervous System.* By CHARLES SHERRINGTON. 1961. Pp. 413. Oxford University Press. Price 16s.

The 1947 re-printing of this classical book has been reproduced by the Yale University Press as a paper-back for just under two dollars. The reproduction in

its paper, printing, and binding is excellent and is heartily recommended to anyone who does not already possess The Integrative Action; teachers should bring it to their students' notice.

*Basalganglien.* By KURT FEREMUTSCH (Bern). Vol. 2, Part 2, Chapter 8. Primatologia. Handbook of Primatology. Ed. by H. Hofer, A. H. Schultz, and Dr. Starck. Pp. 87. Basel: S. Karger. Price Swiss Fr. 27.

The separate reprint of this chapter by an authority upon the morphology of the basal ganglia is most timely. Published in German it gives wide but critical access to the literature upon the comparative anatomy and cytology of the basal grey matter.

*Illustrations of the Nervous System, Atlas III.* By LOUIS HAUSMAN, M.D. Pp. 168. Oxford: Blackwell. Price 76s.

The many clear line drawings in this atlas relate structure to function in most ingenious ways. They are of much educational value, and could form the basis for blackboard illustration.

*Chemical Concepts of Psychosis.* Edited by MAX RINKEL. 1960. Pp. 485. London: Peter Owen Ltd. Price 68s.

The proceedings of the symposium on the chemical concepts of psychosis held in Zurich in the first week of September 1957 at the time of the second International Congress of Psychiatry have been critically edited and presented in a most readable form as a series of essays. As four years have passed since the meetings it is only necessary to bring the volume to the notice of the many interested workers who must have been awaiting its appearance. As a publication, it is a model in its palatable presentation of what could have been indigestible material.

*Neuro-psychopharmacology.* Edited by P. B. BRADLEY, P. DENIKER and C. RADOUCO-THOMAS. 1959. Pp. 727. London: Elsevier Publishing Co. Price £6 15s. 0d.

The First International Congress of Neuropharmacology was held in Rome in September 1958, and the proceedings are presented in full here. In the first part of the book, well-organized symposia upon the study of drug induced behavioural changes in animals and man are recorded. There are also symposia on more general topics such as the present state of neuro-chemistry, and the effect of the advances in pharmacological treatment of psychotic patients upon psychiatric institutions and their extra mural clinics.

The second and major part of the volume contains the short communications, which have, however, been very well edited and indexed; very numerous, they range as widely in their subjects as in their sources of origin. Quite evidently, though extremely expensive, this volume is an excellent source of reference in a rapidly changing field.

*Der Liquordruck.* By Dr. R. HEMMER. 1960. Pp. 82. Stuttgart: Georg Thieme Verlag. Price DM 16·80.

A study of the hydrodynamics of the cerebrospinal fluid, and of the underlying physical and vasomotor changes responsible for normal variations and pathological changes, has been made in the neurosurgical Department of Freiburg University. The experimental procedure and results form the basis for this paperbacked monograph.

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*A Stereotaxic Atlas of the Diencephalon of the Cat.* By HERBERT H. JASPER and COSIMO AJMONE-MARSAN. Has been reprinted and is available for the price of $10 from the following address: National Research Council, Sussex Drive, Ottawa 2, Canada.

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## NOTICE

AN International Symposium on Stereoencephalotomy (Stereotaxic Brain Surgery) was held at Temple University Medical Center, Philadelphia, on October 11 and 12, 1961. Nearly 500 neurosurgeons and brain specialists attended including speakers, exhibitors and guests from Argentine, Canada, England, France, Germany, Holland, India, Japan, Mexico, Peru, Scotland, and Switzerland.

AN International Society for Research in Stereoencephalotomy has been founded and the following officers have been elected:

President: E. A. Spiegel (Philadelphia, Pa.).

Vice-President: T. Riechert (Freiburg, Germany).

Secretary-Treasurer: H. T. Wycis (Philadelphia, Pa.).

The Transactions of the Society will be published in Confinia Neurologica (Publisher: S. Karger, Basel, Switzerland). Further information may be obtained from Dr. H. T. Wycis, 3401 N. Broad Street, Philadelphia 40, Pa.

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